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TREATMENT OF MASSIVE HEMORRHAGE DUE TO PEPTIC ULCER

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MINNEAPOLIS

There is no general agreement among internists on the question of withholding or giving food to patients with bleeding peptic ulcer. Most clinicians advocate a period of fasting, the giving of fluids and transfusions when needed and rest. Allen and Benedict [1] reported 138 cases of massive hemorrhage with a mortality of 14.5 per cent. This did not, however, include gross hemorrhage of mild and moderate degree, the mortality of all patients treated for gross hemorrhage being less than 2 per cent. Goldman [2] noted 40 deaths in 349 cases of gross hemorrhage, a mortality of 11.5 per cent. Eggleston [3] treated 95 patients without a fatality. Hinton [4] reported 52 cases, with a 20 per cent mortality; Westermann,[5] 50 cases with a 20 per cent mortality; Hendon,[6] 46 cases with a 19 per cent mortality, and Manheim,[7] 101 cases with an 8.9 per cent mortality for patients submitted to surgical procedure and a 4.1 per cent mortality for medically treated patients.

Ross [8] reported 187 cases with 6.5 per cent mortality; Aitken,[9] 255 cases with 11 per cent; Bulmer,[10] 578 cases with 10.7 per cent:

From the Medical Service of Long Island College Hospital, Brooklyn.

1. Allen, A. W., and Benedict, E. B.: Acute Massive Hemorrhage from Duodenal Ulcer, Ann. Surg. **98**:736, 1933.

2. Goldman, L.: Gross Hemorrhage from Peptic Ulcer: Its Morbidity, Mortality and Treatment, J. A. M. A. **107**:1537 (Nov. 7) 1936.

3. Eggleston, E. L.: Critical Review of Five Hundred Cases of Gastric and Duodenal Ulcer, J. A. M. A. **75**:1542 (Dec. 4) 1920.

4. Hinton, J. W.: Hemorrhage in Peptic Ulcer, Ann. Surg. **101**:856, 1935.

5. Westermann, J. J.: Bleeding Gastric and Duodenal Ulcers, Ann. Surg. **101**:1377, 1935.

6. Hendon, G. A.: The Treatment of Hemorrhage Caused by Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **2**:255, 1935.

7. Manheim, S. D.: The Incidence and Prognosis of Hemorrhage as a Complication of Gastroduodenal Ulcer, M. J. & Rec. **124**:98, 1926.

8. Ross, K.: The Treatment of Haemorrhage from Peptic Ulcers, M. J. Australia **1**:168, 1930.

(Footnotes continued on next page)

Babey,[11] 82 cases with 4.8 per cent; Chiesman,[12] 191 cases with 25 per cent; Davies and Nevin,[13] 391 cases with 21.0 per cent; Burger and Hartfall,[14] 137 cases with 22 per cent; Gordon-Taylor,[15] 21 per cent mortality; Paterson,[16] 100 cases with 4 per cent mortality; Hellier and Camb,[17] 202 cases with 13 per cent; Cullinan and Price,[18] 105 cases with 18.1 per cent and Bolton, Conybeare and their co-workers,[19] 600 cases with 2.5 per cent. Lynch [20] reported on 31 medically treated patients with a mortality of 12.9 per cent and 21 surgically treated patients with a mortality of 42.8 per cent.

It is interesting to note that the mortality rates from Guy's Hospital, London, reported by three different investigators, varied from 2.5 to 22 per cent. These rates pertained to patients treated in essentially the same manner but from different services. Hence the wide variation can best be explained by assuming that the criteria defining gastric hemorrhage differed from service to service.

In 1906 Lenhartz [21] discussed a new therapy for bleeding ulcers; it differed from that generally in use in that patients were fed eggs and milk immediately. He treated 146 patients, with a mortality of 2.14 per cent. This appears to be the first instance recorded in the literature in which patients with bleeding peptic ulcer were given feedings at once as a part of their treatment.

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9. Aitken, R. S.: Treatment of Profuse Bleeding from the Stomach and Duodenum, Lancet **1**:839, 1934.

10. Bulmer, E.: Mortality from Hematemesis: Supplementary Analysis, Lancet **2**:720, 1932.

11. Babey, A. M.: The Incidence, Mortality and Treatment of Hemorrhage in Gastric, Duodenal and Anastomatic Ulcer, Guy's Hosp. Rep. **86**:129, 1936.

12. Chiesman, W. E.: Mortality of Severe Hemorrhage from Peptic Ulcers, Lancet **2**:722, 1932.

13. Davies, L., and Nevin, R.: Prognosis of Hematemesis: Statistical Review, Brit. M. J. **2**:858, 1934.

14. Burger, G., and Hartfall, J.: Hematemesis in Peptic Ulcer, Guy's Hosp. Rep. **84**:197, 1934.

15. Gordon-Taylor, G.: Attitude of Surgery to Hematemesis, Lancet **2**:811, 1935.

16. Paterson, J. H.: The Treatment of Severe Gastric and Duodenal Hemorrhage, Proc. Roy. Soc. Med. **17**:2, 1924.

17. Hellier, F. F., and Camb, M. A.: Etiology and Mortality Rate of Hematemesis, Lancet **2**:1271, 1934.

18. Cullinan, E. R., and Price, R. K.: Hemorrhage Following Peptic Ulceration, St. Barth. Hosp. Rep. **184**:213, 1932.

19. Bolton, C.; Conybeare, J. J.; Pyrah, L. N., and Cooke, A. M.: Discussion on the Prognosis of Peptic Ulcers, Proc. Roy. Soc. Med. **27**:225, 1934.

20. Lynch, R.: An Analysis of Ulcer of the Stomach and Duodenum, Canad. M. A. J. **17**:677, 1927.

21. Lenhartz, H.: Ueber die Behandlung des Magengeschwürs, Mitt. a. d. Hamb. Staatskrankenanst. **6**:345, 1906.

From Copenhagen Meulengracht [22] reported a series of 251 cases of severe hematemesis and melena with a mortality of 1 per cent. These patients were given a full puréed diet together with alkalis, administration starting on the day after admission. They were fed five times a day such foods as meat balls, timbales, broiled chops, omelet, mashed potatoes, vegetables au gratin, vegetable purées, vegetable soups, creamed vegetables, steamed apricots, applesauce, gruel, rice and tapioca pudding. No restrictions were placed on appetite.

Bernstein,[23] at the Jewish Hospital, Brooklyn, treated 28 patients with hemorrhage due to peptic ulcer, using a modified Andresen diet, without a fatality.

Carlson [24] demonstrated that active peristalsis and secretion take place in an empty stomach. Andresen,[25] at the Long Island College Hospital, based his treatment on these well known physiologic facts, reasoning that a stomach partly filled with food which combines rapidly with any gastric secretion is preferable to an actively contracting stomach full of secretions, which are likely to digest the clots plugging the bleeding vessel or the injured vessel wall itself.

In view of the discussion aroused by the recent paper of Meulengracht, whose results in feeding patients with hemorrhage due to peptic ulcer have just been cited, an exposition of Andresen's work should be of wide interest.

All patients with hematemesis and melena due to peptic ulcer admitted to the Long Island College Hospital are fed immediately and repeatedly. This treatment has been employed for all ward patients and for a majority of the private patients admitted to Long Island College Hospital during the last eighteen years.

The treatment was devised by Andresen in 1916. He first gave gelatin mixtures to patients recovering from gastroenterostomy. The results in these cases were so favorable that the same mixture was given to patients with gastric hemorrhage.

For purposes of comparison, mortality rates for series of cases reported here and abroad are given in table 1.

TREATMENT AT LONG ISLAND COLLEGE HOSPITAL

In the therapy for bleeding ulcer carried out at Long Island College Hospital there are four objectives: (1) stoppage of bleeding by

22. Meulengracht, E.: The Treatment of Hematemesis and Melena with Food, Lancet **2**:1220, 1935.

23. Bernstein, B. M.: Experimental and Clinical Study of Hematemesis Due to Ulcer, M. Rec. **144**:178, 1936.

24. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

25. Andresen, A. F. R.: The Treatment of Gastric Hemorrhage, J. A. M. A. **89**:1397 (Oct. 22) 1927.

formation of clots at the site of the hemorrhage; (2) prevention of an increase in blood pressure (already low as a result of hemorrhage) so rapid as to dislodge these clots; (3) management of shock, with avoidance of too much stimulation, which often results in recurring hemorrhage, and (4) prevention of digestion, by gastric secretion, of the exposed wound in the blood vessel or of the clots filling the defect.

Rest is essential if any of these objectives is to be realized. The patients must have absolute rest in bed and must be constantly reassured, lest fear and its resultant restlessness upset the entire regimen. Patients are usually morphinized for twenty-four hours, or longer if necessary, the interval depending on the course of illness.

TABLE 1.—*Mortality Rates of Hemorrhage Due to Peptic Ulcer*

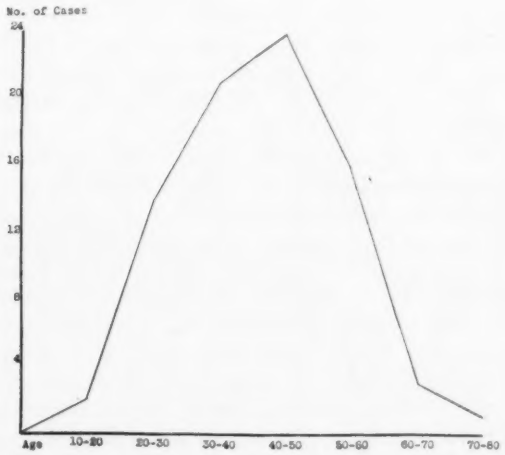
Author	Place	Number of Cases	Death Rate, Percentage
	Treatment by Immediate and Repeated Feedings		
Lenhartz	Not stated	146	2.14
Meulengracht	Copenhagen	251	1.0
Bernstein	Jewish Hospital, Brooklyn	28	0
	Treatment by Period of Starvation		
Allen and Benedict	Massachusetts General Hospital	138	14.5
Goldman	San Francisco General Hospital	349	11.5
Westermann	St. Luke's Hospital, New York	50	20.0
Eggleston	Michigan	96	1.0
Manheim	Mount Sinai Hospital, New York	101	(total) 8.9 (medical) 4.2
Hendon	Louisville, Ky.	46	10.0
Hinton	Bellevue Hospital, New York	52	20.0
Lynch	Montreal General Hospital (medical)	31	12.9
	(surgical)	21	42.8
Ross	Australia	187	6.5
Aitken	London Hospital	255	11.0
Bulmer	Birmingham, England	578	10.7
Babey	Guy's Hospital	82	4.8
Burger and Hartfall	Guy's Hospital	137	22.0
Bolton, Conybeare and others	Guy's Hospital	600	2.5
Chiesman	St. Thomas' Hospital	191	25.0
Davies and Nevin	St. Thomas' Hospital	391	21.0
Gordon-Taylor	Middlesex Hospital	Not stated	21.0
Hellier and Camb	Leeds	202	13.0
Cullnan and Price	St. Bartholomew's Hospital	105	18.1
Paterson	London	100	4.0

The use of coagulants has been largely discontinued after a test period of several years, during which thromboplastin, horse serum, rabbit serum and human serum were found to have no noticeable effect.

Transfusions, intravenously administered fluids and clyses are rarely employed. Occasionally there are patients with obvious signs of a dangerously low blood volume, such as a feeble thready pulse, air hunger and markedly reduced blood pressure; they are given 150 to 200 cc. of blood by transfusion, which carries them out of shock. Intravenous injections of dextrose and clyses are withheld. Seven to ten days after hemorrhage, when there is no apparent danger of recurrent bleeding, one or more transfusions of 500 cc. of blood are of the greatest value and may materially shorten the period of convalescence.

Shock is combated with absolute rest in bed, heat, morphine and restoration of the blood volume, as just indicated. Stimulants are given rarely and with great caution, lest the patient's activity be increased enough to cause another hemorrhage. The surface of the body is kept warm with heaters, hot water bags and blankets. Nothing that might cause chilling, such as the use of ice bags over the epigastrium, is employed.

After hemorrhage the stomach is empty or is filled with blood, which is usually clotted. The blood, with its high protein content, acts as a powerful stimulant for the production of gastric juice, which rapidly digests the blood and may attack newly formed clots or even the injured wall of the blood vessel.



The age incidence in this series is roughly indicated by the graph. Seventy-five per cent of the patients were between 30 and 60 years of age. The largest single age group of those with hemorrhage, constituting 30 per cent of the cases, ranged from 40 to 50 years.

Emesis, melena and retching, always exhibited in some degree, indicate irritability of the gastrointestinal tract. The diet employed is designed to overcome this irritability and hypersecretion.

During the first two days after hemorrhage, 4 ounces (118 cc.) of a solution of gelatin half the strength used for making jelly, with added lactose and orange juice, is fed every one and one-half to two hours. Cereal, gruel, milk, lactose and cream mixtures may be added on the third day if there is no further sign of hemorrhage. A regular diet for patients with ulcer is instituted within a week to ten days after

hemorrhage. Thus a fluid intake of 1,920 cc. is assured each day, with a minimum intake of 1,000 calories.

As the work of Carlson has shown, an empty stomach is never at rest; it appears desirable to keep the stomach as nearly at rest as possible by keeping it partly full. The diet just described is adequate in this respect, is soothing and combines rapidly with any gastric juice that may be present. Giving the gelatin mixture lessens the distressing thirst exhibited by the patients and supplies some nourishment. Roentgenograms are usually taken seven to ten days after bleeding ceases.

In table 2 are given the character and schedule of feedings. Table 3 describes the diet for patients with ulcer, and in table 4 is summarized the routine treatment for all patients with bleeding peptic ulcer.

STATISTICS FROM LONG ISLAND COLLEGE HOSPITAL

The patients with gastric hemorrhage admitted to the Long Island College Hospital from 1925 to 1936 inclusive and treated by Andresen's modified Lenhartz regimen were studied with respect to sex incidence, previous history of ulcer, previous hemorrhage, type of ulcer, evidence of hemorrhage, gastric acidity and mortality. Only the 82 patients who appeared, according to all accepted criteria, to have genuine ulcers were included. Each case was considered from the point of view of history, physical examination, roentgen examination and laboratory studies. In 17, or 20 per cent, of these cases roentgen study failed to reveal evidence of ulcer, but the gastrointestinal series were made from two to six weeks after all signs of bleeding had disappeared and the ulcers had had time to heal. In 7 of these cases there were no symptoms prior to hemorrhage; in the other 10 there were chronic gastric complaints. Duodenitis was ruled out in these cases by fluoroscopic studies.

All the patients had had bleeding severe enough to force them to seek hospitalization, and all had bled shortly before entry. Red cell counts made on admission were less than 3,000,000, and hemoglobin levels were less than 60 per cent. Seventy-six patients exhibited symptoms and physical signs of severe hemorrhage on admission, i. e., restlessness, nausea, tenesmus, thirst, rapid shallow respiration, pallor, low blood pressure, syncope and collapse. The remaining 6 had these symptoms in a lesser degree at some time during their stay in the hospital.

Accepted criteria for hemorrhage from the gastrointestinal tract were hematemesis or melena or both. Of the 54 patients found to have duodenal ulcer, 2 had vomited blood, 13 had passed tarry stools and 39 had done both. The 11 patients with gastric ulcer both vomited blood and passed tarry stools. In the 17 cases in which the site of the ulcer was not definitely found, there were 4 instances of hematemesis, 1 of tarry stools and 12 of both. Thus, of the 82 patients 75 per cent had a

TABLE 2.—*Long Island College Hospital Diet for Patients with Gastric Hemorrhage*

Character of Feedings		Ounces	Grams	Calories
Gelatin solution	Gelatin	1	30	128.0
	Lactose	3	90	360.0
	Juice of 1 orange			
	Water	32	1,000	47.8
Gruel mixture 1	Cereal gruel (oatmeal, barley or cornmeal)	16	500	338.5
	Milk	14	420	290.8
	Cream	4	120	456.9
	Lactose	3	90	360.0
Gruel mixture 2	Cereal gruel (same)	12	350	227.5
	Milk	32	1,000	692.0
	Cream	4	120	456.9
	Lactose	4	120	480.0

Schedule of Feedings		Ounces	Total Calories
First and second day; feed every 1½ hours	Gelatin solution	4	947.2
Third day; feed every 1½ hours	Gelatin solution	4	1,365.4
	Gruel 1	5	
Fourth day; feed every 1½ hours	Gelatin solution	5	1,499.3
	Gruel 1	5	
Fifth and sixth day; feed every 1½ hours	Gelatin solution	6	3,600.0
	Gruel 2 *	6	
Seventh and eighth day; feed every 2 hours	Gelatin solution	6	3,600.0
	Gruel 2 *	6	
Ninth day and thereafter	Long Island College Hospital diet for patients with ulcer		

* Add to gruel mixture at each feeding one of the following: 3 oz. cereal, 1 soft poached egg, custard or jello.

TABLE 3.—*Long Island College Hospital Diet for Patients with Ulcer*

Breakfast	Milk, 8 ounces, with cream if desired; cereal, 5 ounces, with milk or cream; egg, 1, soft boiled or poached; fruit juice or stewed fruit (end of meal)
Midmorning meal	Milk, 8 ounces; cream, ½ ounce; lactose, ½ ounce, with cocoa if desired, always with crackers, toast, bread or cake
Luncheon	Milk, 8 ounces; baked or mashed potato or plain spaghetti; egg, 1, soft boiled or poached, or cream cheese; bread and butter, 2 slices; pudding, custard, gelatin, ice cream or stewed fruit
Midafternoon meal	Same as midmorning meal
Supper	Same as breakfast or luncheon
Bedtime meal	Same as midmorning meal; repeat every 2½ hours during night if awake
Medication	Olive oil, ½ ounce, three times a day before meals; liquid petrolatum, ½ ounce, every night; water as desired

TABLE 4.—*Routine Management of Patients with Gastric Hemorrhage*

I. Keep patient quiet by ordering enough morphine to prevent thirst; bromides and chloral hydrate, given by rectum, may also be administered

II. Order gastric hemorrhage diet (see table 2)

III. Type patient's blood, obtain donors, match blood

IV. Give no blood transfusions until after first week, unless indicated by air hunger, imperceptible pulse or markedly lowered blood pressure

V. Determine red cell count and hemoglobin content every 2 days, more often if hemorrhage persists

VI. Determine coagulation and bleeding time every 2 days and before and after transfusion

VII. Make no efforts at moving bowels for 3 days; on fourth night order warm oil enema (5 ounces to be retained), to be followed by small soapsuds enema on the next day if necessary; continue oil enema every night if needed

VIII. Test stools daily for occult blood until reactions are negative

IX. Avoid the following measures:
1. Giving of ice, food or medicaments by mouth, except as indicated
2. Sudden increase in blood volume by parenteral administration of fluids, except as noted in IV
3. Raising blood pressure by use of epinephrine, ergot or blood stimulants, except in case of severe shock, when stimulants can be given coincidentally with transfusions
4. Lowering of patient's body temperature and increase of shock by use of ice bags

X. Keep patient warm

history of hematemesis and melena, 17 per cent of tarry stools alone and 7 per cent of hematemesis alone.

Of these 82 patients, 58, or 70 per cent, were men and 24, or 30 per cent, were women. Fifty-four, or 66 per cent, had duodenal ulcer; 11, or 13 per cent, had gastric ulcer, and in 17, or 20 per cent, the site of bleeding was not found by roentgen examination. There was a previous history suggestive of ulcer in 72 cases, or 87 per cent, but in 10 cases, or 12 per cent, the hemorrhage was the first symptom noted by the patient. In 33 cases, or 40 per cent, there was previous hemorrhage; but in 49, or 60 per cent, there was no history of bleeding. In 12, or 14 per cent, the patients had previously been admitted to Long Island College Hospital for hemorrhage.

Gastric analyses were done in 49 of the cases studied. In 27, or 56 per cent, an excessive amount of free hydrochloric acid was found, and the curve over the two hour period remained elevated; in 16, or 32 per cent, approximately normal curves were observed, and in 5, or 10 per cent, the acidity was low. All the patients in this last group were at least 50 years old.

Transfusions were given to 17, or 20 per cent, of the patients within one to ten days after admission and to 5 of the patients who died. Another 17 patients received blood before they were discharged, but not until all signs of hemorrhage had disappeared and in no instance before the lapse of ten hospital days. The stools gave a positive benzidine reaction for from five to thirty days after entry.

All patients were examined for foci of infection, extraction of teeth and tonsillectomy being done when necessary. For the 10 patients readmitted for hemorrhage, foci were checked and corrected when necessary at the time of first admission.

One patient had had a posterior gastroenterostomy eighteen years prior to his admission for hemorrhage, and another had a similar procedure six months before his readmission for hemorrhage, the first operation having been performed three weeks after his initial hemorrhage. Two patients had a posterior gastroenterostomy after all signs of bleeding had disappeared.

None of the patients who died was operated on; in the 2 cases in which consent for autopsy was secured, the character and site of the lesions precluded any successful surgical procedure, in the opinion of the pathologist, internist and surgeon who were present at the autopsies.

Of the 82 patients, 8 died, 7 as a direct result of repeated hemorrhage. Three of these fatalities are not included in the mortality statistics because 1 patient died of pneumonia (contracted six weeks after entry) and 1 in the accident room ten minutes after admission, and 1 was not given feedings. Hence the mortality is 6.3 per cent.

One patient lived eight days after admission; the other 4, an average of twenty-six hours after the onset of their hemorrhage. The fatalities, except in the case of a 24 year old man who died in the accident room, occurred between the ages of 40 and 70 years.

Of the 5 cases in which death supervened, in only 1, case 3, was the Andresen therapy strictly followed. Patient 6 did not have an acute gastric hemorrhage; he had tarry stools for three weeks, and the diagnosis of bleeding ulcer was not definitely established, carcinoma of the stomach being the more probable lesion. Patient 5 was exsanguinated on admission and died twenty-four hours later. Patient 4 died after a massive transfusion (not advocated here), and patient 2 was given 500 cc. of a 5 per cent solution of dextrose intravenously. Thus the mortality rate in cases in which the regimen outlined was strictly followed is only 1.3 per cent.

REPORT OF CASES IN WHICH DEATH OCCURRED

CASE 1.—P. A., a 55 year old Italian longshoreman, was admitted to the surgical ward with a history of hematemesis twenty-four hours prior to entrance. Two days later he vomited 200 to 300 cc. of bright red blood. He was then placed on the regimen for gastric hemorrhage, but on the twelfth day in the hospital he again vomited bright red blood. He apparently responded well to treatment, and there were no further signs of bleeding.

On the twenty-second hospital day bronchopneumonia developed. Two days later evidence of cardiac decompensation appeared. The pneumonia failed to respond to treatment, and the patient died on the thirty-sixth day after his admission, without any further signs of hemorrhage. Permission for autopsy was refused.

This case is not included in the compilation of mortality statistics, since the patient died of pneumonia after the gastric hemorrhage had been well controlled.

CASE 2.—J. C., a 72 year old Italian man, was admitted to the hospital with a history of hematemesis twenty-four hours prior to entry. On admission the patient was moribund and in shock, with cold, clammy skin, imperceptible pulse and shallow respirations. The blood pressure was 90 systolic and 60 diastolic. The red cell count was 4,950,000 and the hemoglobin content 112 per cent, the latter falling to 42 per cent a few hours later. Stimulants and sedatives were administered, and the patient was given 500 cc. of a 5 per cent solution of dextrose. He continued to vomit coffee grounds material and passed several tarry stools. He died sixteen hours after admission, without having been given the usual treatment for hemorrhage.

Autopsy disclosed that the stomach was distended. The mucosa was coated with disorganized blood and mucus. No ulcer was observed in the stomach. The duodenum showed several small ulcers about 3 cm. below the pylorus.

This patient was given 500 cc. of a 5 per cent solution of dextrose intravenously, a measure contraindicated in the therapy described here.

CASE 3.—J. K., a 41 year old man, was admitted to the hospital with a history of passing two or three tarry stools a day for three days before entry. Physical examination gave essentially normal results. The blood pressure was 108 systolic and 70 diastolic. The red cell count was 2,000,000 and the hemoglobin content 44 per cent. The regimen for gastric hemorrhage was started, but eighteen hours later the patient vomited about 1,000 cc. of dark red clotted blood. He was given 200 cc. of blood by transfusion but died fourteen hours later.

At autopsy the stomach contained about 600 cc. of thin reddish black blood; the rugae were prominent, and the mucosa was stained bright red. An ulcer, 1.5 cm. in diameter, was observed at the pylorus, at the line of transition between the duodenum and the gastric mucosa. The mucosal margin of the ulcer was soft and overhung the base of the ulcer, which was formed by dense fibrous tissue from a few millimeters to a centimeter thick. The gastroduodenal artery extended across the center of the base of the ulcer. Lateral erosion of its wall was noted; this admitted a probe 3 mm. in diameter. The remainder of the duodenum was normal.

In this case autopsy revealed a pathologic condition not amenable to surgical treatment.

CASE 4.—G. C., a 48 year old Italian longshoreman, was admitted to the hospital with a history of vomiting a pint (473 cc.) of bright red blood one hour prior to entry. Two years previously a series of roentgen examinations of the gastrointestinal tract failed to reveal any pathologic change.

Physical examination revealed cyanosis. The blood pressure was 70 systolic and 50 diastolic. The red cell count was 3,100,000 and the hemoglobin content 70 per cent. The Wassermann reaction was 4 plus. Hematemesis occurred twelve times during the patient's first twenty-four hours in the ward. A transfusion of 500 cc. of blood was given; the patient died eight hours later. Permission for autopsy was refused.

In this case a massive transfusion was given, a procedure contraindicated if the tenets of therapy advocated by Andresen are to be followed strictly.

CASE 5.—D. L., a 41 year old Italian man, vomited a quart (946 cc.) of bright red blood twenty-two hours before entry to the hospital and passed several tarry stools. Physical examination revealed that he was cadaverous, with a cold clammy skin. The blood pressure was 120 systolic and 80 diastolic. The red cell count was 850,000; the hemoglobin content was 10 per cent. A transfusion of 250 cc. of blood was given, but twenty-four hours later the patient went into shock and failed to respond to treatment. Permission for autopsy was refused.

Since this patient was exsanguinated on admission and died within twenty-four hours, the data might have been excluded from the mortality statistics.

CASE 6.—J. K., a 52 year old man, entered the hospital with a history of passing one or two tarry stools a day for three weeks prior to entry. Physical examination gave essentially normal results. The blood pressure was 100 systolic and 80 diastolic. The red cell count was 4,430,000 and the hemoglobin content 74 per cent.

The patient was given the routine treatment but complained bitterly of gastric pain. On the fourth day he vomited about a pint of coffee grounds material. He continued to vomit two or three times a day for the next week, sometimes raising food just eaten and sometimes brownish material. On the eighth hospital day the patient vomited all feedings and went into shock. He died twelve hours later, despite treatment. Permission for autopsy was refused.

In this case the diagnosis of bleeding peptic ulcer was never firmly established, carcinoma being more likely.

CASE 7.—B. S., a 68 year old housewife, who had been discharged from the hospital one week previous to the present admission after recovery from gastric hemorrhage, was readmitted after she had begun to pass tarry stools. Physical examination revealed that she was pale, stuporous and moribund. The blood pressure was 124 systolic and 80 diastolic. The red cell count was 1,000,000 and the hemoglobin content 35 per cent. The patient was given 500 cc. of blood by transfusion, but shortly afterward she went into shock; she died sixty hours after readmission. Consent for autopsy was refused.

This patient was not given the feedings for gastric hemorrhage. A transfusion of 500 cc. was given one hour before death.

CASE 8.—I. V., a 24 year old Mexican man, was brought into the hospital by the ambulance surgeon with a history of having vomited copious quantities of bright red blood. Physical examination revealed that he was in extreme shock. He died ten minutes later, before any treatment could be given. Permission for autopsy was refused.

This patient died in the accident room before any form of treatment could be given.

COMMENT

All methods of treating gastric ulcer emphasize the need for absolute rest and the use of opiates when necessary. Aside from this general concurrence, treatment varies widely, some authorities insisting that fluids given parenterally and transfusions are essential, others that fluids of all sorts are contraindicated. Most clinicians prefer a period of fasting, while Lenhartz, Andresen and Meulengracht stated that they advocate feedings.

The rationale of feeding patients with bleeding ulcer has already been discussed. It is, however, pertinent to note again that an empty stomach contracts actively and produces gastric secretion. Since the purpose of any treatment is primarily the stopping of hemorrhage, it is reasonable to strive to keep the stomach as completely at rest as possible. Equally important is the inactivation of potent gastric secretions which may digest clots formed in the bleeding vessel or the vessel wall itself.

All these criteria seem to be met best by the diet outlined by Andresen, which is given in frequent small feedings and consists of a bland gelatin mixture capable of combining rapidly with the gastric juices.

The distressing thirst of which the patients complain is greatly lessened by the feedings, and no amount of reassurance is so effective in quieting their worry as the giving of nourishment so soon after hemorrhage. Early feedings are believed to be important in lessening the length of hospitalization, which averages twenty-seven and one-half days at Long Island College Hospital.

Fluids are not given intravenously and parenterally, the desirability of the procedures being far outweighed by the danger of increasing the blood pressure to a point high enough to dislodge clots already formed. When possible, transfusions are avoided early in the treatment for the same reason, but they are given in 200 to 300 cc. portions when it is believed that the patient is dying for lack of blood. Occasionally one such transfusion will carry a patient past the danger point, but it is again emphasized that transfusions are reserved for the exsanguinated, moribund patient and are not given routinely.

Of the 7 patients who died directly as a result of continued bleeding, 5 received transfusions or fluids (in 3 cases in amounts not advised here). Seventeen patients were given small transfusions before the tenth hospital day. After all signs of hemorrhage have disappeared, blood is administered with great benefit and may shorten the period of hospitalization by several days.

When various mortality statistics are compared, variations of from 1 to 20 per cent are found, the rate being consistently higher whenever there was surgical intervention. Thus, at one hospital 5 of 7 patients subjected to operation died; at another all died. It is indeed rare that an acutely bleeding patient recovers after a surgical procedure. As the mortality of the operation itself is higher than the mortality to be expected from conservative treatment of bleeding ulcers, this form of therapy should be reserved for the unusual patient. The operation, once performed, affords no guarantee of freedom from recurrent hemorrhage, for Balfour [26] found that 13 per cent of all patients had recurrent bleeding after operation. Hinton, Westermann and Hurst [27] also observed recurrent hemorrhage after surgical procedures. Lynch reported on 21 patients surgically treated, with a mortality of 42.8 per cent, and on 31 medically treated, with a mortality of 12.9 per cent.

Taken alone, the mortality of 6.3 per cent at Long Island College Hospital is no brief for the treatment of bleeding ulcers by immediate and repeated feedings, but when considered with the 2.1 per cent mortality reported by Lenhartz, the 1 per cent mortality of Meulengracht and the 0 per cent mortality of Bernstein it becomes significant. It is

26. Balfour, cited by Hurst.[27c]

27. (*a*) Hinton.[4] (*b*) Westermann.[5] (*c*) Hurst, A. F.: The Incidence, Mortality and Treatment of Hemorrhage in Gastric, Duodenal and Anastomatic Ulcer, Guy's Hosp. Rep. **86**:135, 1936.

noted in table 1 that mortality rates vary from 1 to 25 per cent, for patients deprived of food, but only five investigators reported a mortality below 6.3 per cent.

It may be concluded that a certain percentage of patients with bleeding ulcer will die, regardless of treatment, but the fundamentals of therapy must be met by aiding the physiologic processes of healing. This can best be done by putting the stomach as nearly at rest as possible, inactivating the gastric secretions and maintaining the general body nutrition. The modified Lenhartz regimen of Andresen meets all these criteria physiologically and will, it is hoped, find a deservedly wider use in the future.

SUMMARY

Eighty-two patients with hemorrhage due to ulcer were admitted to Long Island College Hospital from 1925 to 1936; 54, or 66 per cent, had duodenal ulcer; 11, or 13 per cent, gastric ulcer, and in 17, or 20 per cent, the site of hemorrhage was not found by roentgen study.

Treatment in all cases included rest in bed, administration of morphine and immediate and repeated feedings as outlined. Parenteral injection of fluids was withheld, and transfusions were given only as indicated.

Of the 79 patients for whom the mortality rate is computed, 5, or 6.3 per cent, died as a result of continued bleeding. Of patients who were given the exact form of treatment outlined, only 1.3 per cent died.

Autopsy in 2 cases revealed pathologic conditions not amenable to surgical intervention.

Dr. Andresen and Dr. D'Albora gave encouragement and criticism.

Minneapolis General Hospital.

A CRITICAL EVALUATION OF GASTRIC ANTACIDS

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A gastric antacid is a chemical substance introduced into the stomach for the purpose of lowering the hydrogen ion concentration, or acidity, of the gastric contents. Such antacids are in common use in medical practice, mostly in the treatment of peptic ulcer, and in addition they are employed extensively in self medication by those who have recognized the efficacy of sodium bicarbonate in the relief of several types of gastric distress. Of the host of substances which are capable of neutralizing acid, only a few are adaptable to use as gastric antacids, and not more than a dozen have received general attention in therapeutic practice.

Unexpected difficulties are often encountered in the use of antacids to lower gastric acidity, because no antacid has yet been found which will simply neutralize acid without exhibiting additional pharmacologic action. These side actions usually have been objectionable rather than desirable. Under these circumstances it is not surprising that the full value of antacids has most frequently been unrealized and that their use has been somewhat discredited. A more complete understanding of the mechanisms by which the antacids act will perhaps help to dispel much of the disagreement and misunderstanding which apparently surround them at present.

The gastric antacids assume their greatest importance in the therapy of peptic ulcer, and their use has been most extensive in this field. As a convenient way of bringing out the physiologic and pharmacologic principles involved, they will be discussed in relation to this disease. It is not the purpose here to defend the use of antacids for peptic ulcer or to give the impression that all difficulties will be avoided by adherence to the conclusions reached, for each patient requires individual analysis and treatment. The fact remains, however, that antacids are used extensively today, and their use on a rational basis must be predicated on a complete knowledge of their limitations and their possibilities, both favorable and unfavorable. Rivers,[1] speaking of peptic ulcer,

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1. Rivers, A. B.: Certain Factors Important in the Etiology and Treatment of Peptic Ulcer, J. M. A. Alabama **6**:166-177, 1936.

stated, "It is unfortunately true that much of what is known is forgotten or ignored when a plan of treatment for the cure of the disease must be formulated." This statement seems to be especially true with regard to the use of antacids. Thus the development of a rationale for the use of the antacids and an evaluation on this basis of the various antacids now available should be worth while.

Antacids are generally conceded to be used for three primary purposes in the treatment of peptic ulcer: (1) to allay pain, (2) to relieve pylorospasm and (3) to avoid digestion and corrosion of a lesion by acid chyme. The first and second of these objectives are usually accomplished by moderate doses if the antacids are effective at all. Simple neutralization of the contents of the stomach at the time of distress is the means by which two objectives are accomplished. The third objective has been the source of most of the trouble resulting when antacids are used. In the first place, the symptomatic relief afforded by the accomplishment of the first two objectives has been deceptive, leading to the supposition that the third objective is automatically attained also. However, the amount of antacid sufficient to relieve pain and pylorospasm is far short of the amount necessary to prevent acid digestion and corrosion of the lesion during the greater part of the time. Perhaps it is unnecessary to neutralize the contents of the stomach completely in order to prevent the deleterious action of acid chyme, and it is beyond question that ulcers do heal even in the presence of a moderate amount of gastric acidity. It is yet to be proved, however, that healing under these conditions is not further evidence of the remarkable ability of the physiologic economy to effect recovery even though under a handicap and that recovery would not be facilitated by the practical absence of free acid.

SIPPY POWDERS

In 1915 Sippy [2] promulgated a plan of treatment of peptic ulcer based on the principle of continuous prevention of acid corrosion and digestion of the lesion by the use of a bland diet and a mixture of antacid powders. The diet was chosen with the aim of minimizing (1) the chances of trauma, (2) secretory stimulation and (3) gastric emptying time. The powders, consisting of 0.6 Gm. each of sodium bicarbonate and magnesium oxide in powder 1 and 0.6 Gm. of bismuth subcarbonate with 2 to 3 Gm. of sodium bicarbonate in powder 2, were administered alternately every hour. The success attained by this regimen is well known, yet several objectionable features arose in this treatment which caused much modification in the powders by various clinicians.

2. Sippy, B. W.: Gastric and Duodenal Ulcer: Medical Cure by an Efficient Removal of Gastric Juice Corrosion, J. A. M. A. **64**:1625-1630 (May 15) 1915.

The first serious difficulty encountered was the frequent appearance of untoward symptoms, which are now recognized as resulting from the production of systemic alkalosis by absorbable antacids. The following outline of the literature will provide the salient points of the clinical history of the Sippy treatment as a background for the ensuing discussion.

Sippy noticed certain unfavorable symptoms in patients on his regimen, but it was not until 1923 that the first detailed description of the syndrome was published.[3] Symptoms usually begin by the fourth day, but may not appear until weeks after treatment begins.[4] Nervousness, introspection, irritability, anorexia and distaste for milk usually appear first. If the condition becomes worse there are headache, nausea, vomiting, vertigo, pains in joints and muscles, dry skin, dry throat, slow respiration, apathy, tetany, prostration and coma, usually in the order given.[4] Several deaths have been attributed to alkalosis produced by this treatment.[5] The laboratory evidence appears even earlier than the subjective symptoms[6] and is, indeed, often the only evidence by which mild forms can be correctly diagnosed. There is a rise in the carbon dioxide-combining power of the plasma,[7] in the urea[8] and the crea-

3. Hardt, L. L., and Rivers, A. B.: Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, Arch. Int. Med. **31**:171-180 (Feb.) 1923.

4. (*a*) Hardt and Rivers.[3] (*b*) Cope, C. L.: Alkali Poisoning: A Danger in the Treatment of Gastric Ulcer, Brit. M. J. **2**:914-917, 1936. (*c*) Kruse, F. H.: Complications of Peptic Ulcer and Their Treatment, J. A. M. A. **109**:868-874 (Sept. 11) 1937.

5. (*a*) Gatewood, L. C., in discussion on Block, L., and Serby, A. M.: Use of Alkalis in the Treatment of Peptic Ulcer, J. A. M. A. **92**:134-139 (Jan. 12) 1929. (*b*) Youmans, J. B., and Greene, I. W.: Clinical Alkalosis in Gastric Disease, J. Michigan M. Soc. **23**:160-163, 1924. (*c*) Venables, J. F.: Seven Cases of Alkalosis Following Alkaline Treatment of Duodenal Ulcer, Guy's Hosp. Rep. **75**:152-157, 1925. (*d*) Cooke, A. M.: Alkalosis Occurring in the Alkaline Treatment of Peptic Ulcers, Quart. J. Med. **1**:527-541, 1932.

6. (*a*) Gatewood, W. E.; Gaebler, O. H.; Muntwyler, E., and Myers, V. C.: Alkalosis in Patients with Peptic Ulcer, Arch. Int. Med. **42**:79-105 (July) 1928. (*b*) Jeghers, H., and Lerner, H. H.: The Syndrome of Alkalosis Complicating the Treatment of Peptic Ulcer, New England J. Med. **214**:1236-1244, 1936.

7. (*a*) Koehler, A. E.: Acid-Base Equilibrium: I. Clinical Studies in Alkalosis, Arch. Int. Med. **31**:590-605 (April) 1923. (*b*) Hardt and Rivers.[3] (*c*) Kruse.[4c] (*d*) Youmans and Greene.[5b] (*e*) Cooke.[5d] (*f*) Jeghers and Lerner.[6b] (*g*) Grant, S. B.: Tetany: A Report of Cases with Acid-Base Disturbance, Arch. Int. Med. **30**:355-361 (Sept.) 1922. (*h*) Oakley, W.: Alkalosis Arising in Treatment of Peptic Ulcer, Lancet **2**:187-190, 1935. (*i*) Koehler, A. E.: The Effect of Acid and Base Ingestion upon the Acid-Base Balance, J. Biol. Chem. **72**:99-121, 1927. (*j*) Jordan, S. M.: Calcium, Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis, J. A. M. A. **87**:1906-1909 (Dec. 4) 1926.

8. Hardt and Rivers.[3] Kruse.[4c] Venables.[5c] Cooke.[5d] Oakley.[7h]

tinine[9] content and the p_H[10] of the blood and in the nonprotein nitrogen.[11] A decrease occurs in the chloride content of the blood[12] in the sulfate clearance[4c] and in the excretion of phenolsulfonphthalien,[13] and the urine is increased in amount[7h] and in alkalinity.[14] Casts and albumin are often seen,[15] and the chloride content of the urine is low.[4b]

The cause of the syndrome was obscure until Hardt and Rivers proved that milk was not the responsible agent and attributed the causation to absorbable alkaline powders. Sippy powders,[16] sodium bicarbonate alone,[17] sodium and potassium citrates and acetates[18] all have been proved capable of causing the syndrome. Contributing factors are renal insufficiency,[19] pyloric obstruction, vomiting,[20] a diet low in salt,[21] hemorrhage, anemia and impaired hepatic function.[6b] Loss of chloride also is a factor if much gastric residuum is removed by lavage in cases of retention.[7a]

Reports of the incidence of alkalosis in cases of peptic ulcer vary widely, 8 per cent,[22] 10 per cent,[4c] 20 per cent[23] and 47 per cent[6a]

9. Hardt and Rivers.[3] Kruse.[4c]

10. (*a*) Gatewood, Gaebler, Muntwyler and Myers.[6a] (*b*) Koehler.[7i] (*c*) Binger, C. A. L.; Hastings, A. B., and Neill, J. M.: Edema Associated with Moderate Bicarbonate Administration During Convalescence from Pneumonia, Arch. Int. Med. **31**:145-150 (Jan.) 1923. (*d*) Kast, L.; Myers, V. C., and Schmitz, H. W.: Clinical Conditions of Alkalosis, J. A. M. A. **82**:1858-1861 (June 7) 1924.

11. Kruse.[4c] Oakley.[7h]

12. Gatewood, Gaebler, Muntwyler and Myers.[6a] Kruse.[4c] Jordan.[7j]

13. Kruse.[4c] Cooke.[5d] Jeghers and Lerner.[6b]

14. Cope.[4b] Jeghers and Lerner.[6b] Oakley.[7h]

15. Footnote 4. Cooke.[5d] Oakley.[7h]

16. Gatewood, Gaebler, Muntwyler and Myers.[6a] Hardt and Rivers.[3] Cope.[4b] Venables.[5c] Grant.[7g]

17. Koehler.[7a] Oakley.[7h] Kast, Myers and Schmitz.[10d]

18. Cope.[4b] Koehler.[7i]

19. (*a*) Kruse.[4c] (*b*) Venables.[5c] (*c*) Jeghers and Lerner.[6b] (*d*) Kast, Myers and Schmitz.[10d] (*e*) Chace, A. F.: Medical Aspects of Peptic Ulcer with Special Reference to Diagnosis and Treatment, Am. J. Digest. Dis. & Nutrition **1**:866-870, 1935.

20. Kruse.[4c] Jeghers and Lerner.[6b] Ellis, A. W. M.: Disturbance of Acid-Base Equilibrium of the Blood to the Alkaline Side, Quart. J. Med. **17**:405-423, 1924. McVicar, C. S.: A Discussion of the Clinical and Laboratory Findings in Certain Cases of Obstruction in the Upper Gastrointestinal Tract: The Role of Blood Chemistry in Diagnosis, Prognosis, and Treatment of This Condition, Am. J. M. Sc. **169**:224-235, 1925.

21. Jeghers and Lerner.[6b] Chace.[19e]

22. Jordan, S. M., and Kiefer, E. D.: Factors Influencing Prognosis in the Medical Treatment of Duodenal Ulcer, Am. J. Surg. **15**:473-482, 1932.

23. Eusterman, G. B.: Gastric and Duodenal Ulcers: Factors Essential to Their Successful Medical Management, Wisconsin M. J. **34**:473-477, 1935.

having been recorded. This variation is easily accounted for by differences in the dosage and by failure to recognize many cases of alkalosis.[24] The time when the blood is sampled also may lead to variations of data among investigators, since a patient who does not receive powders during the night tends to return to normal by morning. It is probable that when Sippy's recommendations are followed and enough alkaline powders are given to control acidity at all times the incidence is in the higher brackets, while the lower figures obtain in current practice in which the dosage is insufficient to avoid acid corrosion much of the time. On the other hand, it has been pointed out repeatedly [24] that the onset of alkalosis is so insidious and so many of the symptoms are common to other diseases that in a large number of cases the condition, especially when mild, is not recognized. It is easy to overlook the symptoms in the early stages, and the condition may supervene weeks or months after treatment is instituted, even though no change in the dose or the routine has occurred. Hurst [25] said:

> In common with Ryle and Hardy, I have seen patients who were thought to be dying from uraemia, but were really suffering from severe alkalosis, and . . . I believe that more deaths must result from unrecognized poisoning with alkaline powders than from accidental poisoning with the barbiturates.

Mechanism of Action.—The explanation of the manner in which the administration of Sippy powders results in systemic alkalosis brings in a number of factors which have not always been apparent. The same mechanism operates when any absorbable alkali is considered, and thus Sippy powders may be conveniently referred to and should be regarded as an example of a general class of antacids—the systemic or absorbable antacids.

It can be shown by calculating from the data of Freezing, Gibson and Mathews [26] that the average patient following the unmodified Sippy regimen receives in one day antacid powders sufficient to neutralize 5,000 cc. of 0.36 per cent, or 3,600 cc. of 0.5 per cent, hydrochloric acid. The strengths of the acid are significant because 0.36 per cent represents the concentration of acid in the stomach after secreted acid is mixed with other contents of the stomach, while 0.5 per cent is the strength approached by the acid as it is secreted, before it is mixed with other contents. However, it may be safely estimated that the stomach does not secrete more than 2,000 cc. of gastric juice in twenty-four hours (1,500 cc. is probably nearer the upper limit), and even if the

24. Koehler.[7a] Cope.[4b] Youmans and Greene.[5b] Jeghers and Lerner.[6b] Oakley.[7h]

25. Hurst, A. F.: Diseases of the Alimentary Canal, Practitioner **137**:409-422, 1936.

26. Freezing, C. R. E.; Gibson, C. S., and Mathews, E.: A Contribution to the Study of Alkalis as Therapeutic Agents, Guy's Hosp. Rep. **78**:191-198, 1928.

entire 2,000 cc. were 0.5 per cent hydrochloric acid the amount of alkali administered in the same period would greatly exceed that necessary to neutralize this acid. The excess would be sufficient to neutralize at least an additional 1,500 cc. of 0.5 per cent acid. These relations are shown in chart 1.

Notwithstanding the foregoing facts, it must be remembered that Sippy and subsequent workers found by analysis of the gastric contents that the amounts of alkaline powders which they recommended were actually necessary to prevent the appearance of free acid. Wosika and Emery [27] recently investigated the effectiveness of the Sippy regimen in neutralizing the gastric juice, with a powder consisting of calcium carbonate and sodium bicarbonate. Taking samples of the gastric

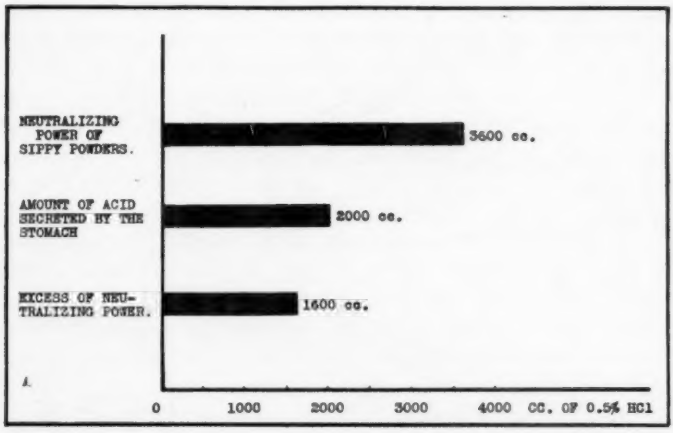

Chart 1.—Total neutralizing power of the Sippy powders given in twenty-four hours (one each hour and four after 7 p. m.) compared with the amount of acid secreted by the stomach in the same time.

contents every half-hour throughout the day, they found that the condition was adequately controlled in only about 57 per cent of their cases, even though their interpretation of control was liberal. The total neutralizing power of all powders given each day in their series was equal to that of 30 Gm. of sodium bicarbonate (unmodified Sippy powders are equivalent to 40 Gm. of bicarbonate per day). In current practice the amounts of antacid given are usually materially less than this. How much more, then, would be the failure to control adequately

27. Wosika, P. H., and Emery, E. S.: The Effectiveness of the Sippy Regimen in Neutralizing the Gastric Juice of Patients If the Amount of Alkali Is Not Varied, Ann. Int. Med. **9**:1070-1077, 1936.

the free acid! Why is an amount of alkaline powder calculated to be adequate insufficient in almost 50 per cent of cases? Reference to chart 2 will help to explain this.

The interrelations of significance when absorbable antacid powders are ingested are indicated in chart 2. The average Sippy powder given by mouth provides each hour 27.5 milliequivalents of base. In addition, a significant amount of acid is neutralized by the milk taken during the hour, and also a small amount is neutralized by secreted saliva. When the antacid reaches the stomach it encounters the acid secreted there.

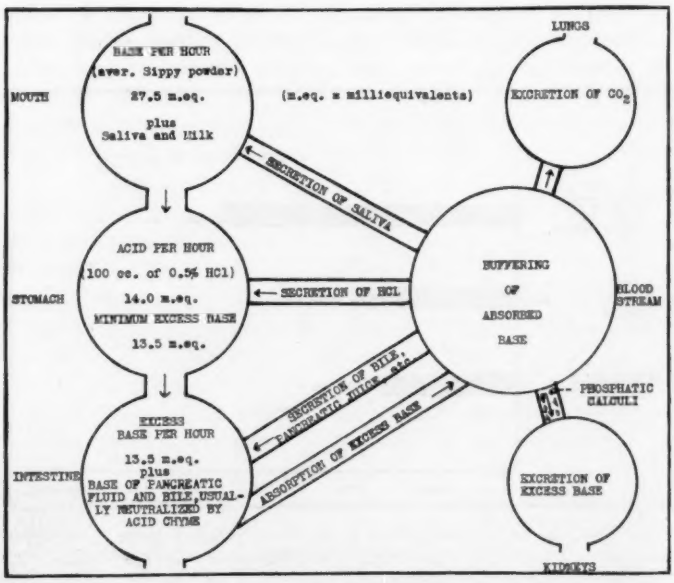

Chart 2.—Interrelations affected when a systemic antacid is ingested.

Ordinarily the amount of acid secreted in one hour approximates 50 cc. of 0.5 per cent hydrochloric acid, yet under the conditions obtaining in cases of peptic ulcer it may be somewhat increased. Suppose then that in one hour the rate is doubled, to 100 cc. of 0.5 per cent hydrochloric acid. This is 14 milliequivalents. In subsequent consideration the antacid value of the milk in the diet and that of saliva will be disregarded, even though it is a significant amount.

From these figures it is seen that the antacid powders provide an excess of base amounting to a minimum of 13.5 milliequivalents each hour. This is termed a *minimum* because the emptying of the stomach is facilitated by the neutralization as the gastric acid reacts with the

antacid. Thus, *much of the antacid leaves the stomach before the hour has elapsed and is not available for the neutralization of acid subsequently secreted during that hour.* It was estimated [27] that the amount of alkaline powder given by the Sippy regimen was 25 to 50 times as much as was used to neutralize acid, chiefly because of this factor.

Another troublesome factor enters here. The production of alkalinity in the stomach has been shown [28] to result in a "rebound" secretion of gastric acid which is greater than is encountered when the contents of the stomach are not made alkaline. It is apparent, then, that while the alkaline powders directly cause their quick passage from the stomach they also cause an increased flow of acid into it after they leave it. A vicious cycle is established—alkaline powders causing increased alkaline reaction in the stomach, alkaline reaction causing increased flow of gastric acid and increased amount of acid requiring larger amounts of antacid for neutralization. Is it not possible that this factor may be the largest contributor to the hyperacidity in many cases of uncomplicated peptic ulcer?

The excess base passes into the stomach, where it is augmented by much alkaline fluid, mostly secreted by the pancreas and liver, which is normally partially neutralized by acid chyme. This alkaline fluid is probably more alkaline in subjects with hyperacidity than in normal persons, since an increase in the alkalinity of the pancreatic secretion during increased secretion of acid has been noted.[29] From these observations it is apparent that potential supply of absorbable base, in some instances large, constitutes the source of the systemic alkalosis, and it probably is superfluous to point out that the danger exists not only when the antacid is a single absorbable alkaline substance or a mixture of such substances but also when the powders are mixtures of absorbable and nonabsorbable substances.

Systemic Alkalosis.—As the blood takes up the excess base from the intestine the buffers in the blood are called into play to resist a change of p_H. With this constant strain toward a more alkaline reaction, the sudden influx of unusually large amounts of base, especially when a pathologic condition of the kidneys delays the excretion of base or when chloride is lost either by vomiting or by repeated washing out of reten-

28. Crohn, B. B.: Effect of Antacid Medication on Gastric Secretion and Acidity, Am. J. M. Sc. **155**:801-819, 1918. Lockwood, B. C., and Chamberlin, H. G.: The Effect of Alkalis on Gastric Secretion and Motility as Measured by Fractional Gastric Analysis, Arch. Int. Med. **32**:74-81 (July) 1923. Boyd, T. E.: Influence of Alkalies on the Secretion and Composition of Gastric Juice, Am. J. Physiol. **71**:455-471, 1925.

29. Neale, A. V., and Klumpp, T. G.: Action of Histamine on the Pancreas, J. Clin. Investigation **9**:197-208, 1930.

tion fluid from the stomach,[7a] the buffers are often unable to cope with the situation, and a change of p_H results. The blood, it may be recalled, is unable to resist a change toward alkalinity as efficiently as it does a change toward acidity, for if the Henderson-Hasselbalch equation,[30] which relates the p_H of the blood to the relative amounts of the acid and the basic form of each buffer pair in the blood, is remembered, it may be shown that for the p_H of the blood to be normal, the p_K values of the buffers in the blood require that the ratio of buffer pairs be on the alkaline side of the point of maximum buffering efficiency in order to satisfy the equation. This means that as base is added the buffering efficiency of the blood is decreasing, while as acid is added the point of maximum buffering efficiency is approached; this point must be passed before an abnormal p_H can result. Since acidosis is seen so often clinically, it should not be surprising to find that the administration of antacids may easily cause alkalosis. In fact, alkalosis can be produced simply by voluntary hyperventilation of the lungs.

Argument.—It is true that most of the difficulties in the use of absorbable alkaline powders would be overcome if the dosage were sufficient to neutralize free acid without producing an alkaline reaction in the stomach. Unfortunately, it is difficult, if not impossible, to strike this balance.[31] Many modifications in the use of Sippy powders have been made with this objective in view, but physiologic conditions make success largely fortuitous and temporary. On the one hand is the Scylla of free acid and on the other the Charybdis of rebound secretion of acid, with no practical guiding points to aid the physician in steering a middle course to avoid these dangers. Analysis of the gastric contents may be made to determine the amount of antacid needed for neutralization at any given time, but gastric acidity varies from hour to hour, day to day and week to week, as disease or recovery progresses. There is no way, short of almost continuous analysis of the gastric contents, to be reasonably sure that the objective of the treatment is attained continuously.[32] Since constant analysis is impractical, there remain three courses which may be followed: 1. The dosage may be decreased so that

30. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1926, p. 426.

31. (*a*) Bloch, L., and Serby, A. M.: Use of Alkalis in the Treatment of Peptic Ulcer, J. A. M. A. **92**:134-139 (Jan. 12) 1929. (*b*) Wosika, P. H., and Emery, E. S.: The Value of a Mixture of Powdered Milk and Alkali for Neutralizing the Gastric Acidity of Patients with Peptic Ulcer, Ann. Int. Med. **9**:1078-1090, 1936. (*c*) Loevenhart, A. S., and Crandall, L. A.: Calcium Carbonate in Treatment of Gastric Hyperacidity Syndrome and in Gastric and Duodenal Ulcer, J. A. M. A. **88**:1557-1559 (May 14) 1927.

32. Bloch and Serby.[31a] Wosika and Emery.[31b]

alkalinity is seldom produced in the stomach. This is done in much current practice, but the third objective of antacid treatment, which has been stated, is then seldom attained. 2. The dosage may be increased to insure that all acid, even the rebound secretion, is neutralized continuously. This results in systemic alkalosis in a high percentage of cases, as has been explained. Also, the constant high alkalinity of the contents of the stomach irritates the ulcer [31c] and is conducive to its chronicity,[33] and it may lead to impairment of the kidneys by the precipitation of sharp crystalline phosfates in the renal tubules when a constantly alkaline urine is produced.[34] 3. The dosage can be adjusted with the hope of obtaining a satisfactory middle course between 1 and 2. The condition is then one of a pendulum-like movement between alkalinity and the presence of free acid, as has been discussed, and the objective is practically impossible to accomplish.

In addition, a number of minor objections are specifically directed at sodium bicarbonate. The most serious of these is that when an ulcer is near perforation the release of carbon dioxide by chemical action of the antacid with gastric acid may lead to dangerous distention which may complete the perforation.[35] This objection would, of course, apply to any antacid capable of releasing carbon dioxide.

Thus, in choosing an antacid it is essential to keep in mind (1) the difference between a systemic and a nonsystemic antacid and (2) the possibility of rebound secretion of acid if the antacid is capable of producing an alkaline reaction in the stomach. Since systemic alkalinization has not been shown to be of value in reducing gastric acidity and since the use of systemic antacids has been shown to be attended often by undesirable and deleterious sequelae, a nonsystemic antacid is rationally indicated as a first choice. Further, when a nonsystemic antacid is chosen, it should be one incapable of producing secondary secretion of acid or other such side effects. If systemic antacids are used, it is rational to give small doses frequently rather than large doses infrequently. This fact probably accounts in some part for the superiority of the results attained by a constant drip apparatus. Such an apparatus has proved efficacious in the use of nonsystemic antacids also.

33. Kreis, L.: Kausale Radikalheilung der Hyperazidität für konservative Behandlung, Wien. med. Wchnschr. **4**:140-141, 1931.

34. (*a*) Hurst.[25] (*b*) Loevenhart and Crandall.[31c] (*c*) Rosenthal, E.: Treatment of Gastric and Duodenal Ulcer, Rev. Gastroenterol. **3**:227-238, 1936. (*d*) Schrijver, J.: The Sippy Treatment of Gastric Ulcer, Nederl. tijdschr. v. geneesk **2**:1757-1772, 1925; abstracted, J. A. M. A. **85**:1848 (Dec. 5) 1925.

35. Hurst, A. F.: Recent Advances in the Treatment of Gastric Disease, Brit. M. J. **2**:779-783, 1928.

NONSYSTEMIC ANTACIDS

The objections to the use of absorbable alkaline substances as gastric antacids have led to a continued search for other substances better suited to this purpose. The progress, to date, consists of the introduction and use of chemical substances, either soluble or insoluble, which are practically unabsorbed from the alimentary canal and which are capable of lowering the free acidity to a desirable point.

Magnesium Salts.—There is relatively little absorption of magnesium salts from the gastrointestinal tract, and the amount absorbed is insufficient to cause toxic effects. Magnesium oxide, carbonate, citrate, hydroxide and peroxide have antacid properties and might be expected to function well as gastric antacids if unmixed with systemic antacids. Unfortunately, however, the irritation and diarrhea which they frequently cause preclude their use except in limited amounts.[36] An equally serious objection to their use arises from the property of stimulating a rebound secretion of acid, a property in which magnesium oxide is surpassed by few drugs.[35] Magnesium phosphate and calcium phosphate, which will be discussed in the next paragraph, were perhaps the first neutral salts to be suggested as antacids to replace Sippy powders. Magnesium trisilicate is included under colloidal substances because of its special nature.

Calcium Salts.—The use of tertiary calcium and magnesium phosphates to replace Sippy powders was suggested in 1923,[37] with reports of adequate control of acidity and no toxic symptoms or disturbance of the systemic acid-base balance. Their action as local antacids only was later confirmed,[38] and their superiority in many respects over absorbable alkaline powders was established. The reaction in the stomach cannot be carried beyond p_H 7 by these salts, and the constipating effect of the calcium may be balanced by the laxative effect of the magnesium. Some objections to their use may be made, however: (*a*) Calcium phosphate is rather ineffectual as an antacid;[39] (*b*) it is often difficult to adjust the dose of each component of a powder so that the laxative and the constipating effect are balanced and yet keep an optimum for the control of acidity; (*c*) the neutral reaction which

36. Bloch and Serby.[31a] Loevenhart and Crandall.[31c]

37. Greenwald, I.: Gastric Antacids Which Cannot Act as Systemic Alkalis, Proc. Soc. Exper. Biol. & Med. **20**:436-439, 1923. Kantor, J. L.: Antacid Gastric Therapy, with Especial Reference to the Use of Neutral Antacids, J. A. M. A. **81**:816-818 (Sept. 8) 1923.

38. Shattuck, H. F.; Rohdenburg, E. L., and Booher, L. E.: Antacids in the Medical Management of Peptic Ulcer, J. A. M. A. **82**:200-203 (Jan. 19) 1924.

39. Crohn, B. B.: The Clinical Use of Colloidal Aluminum Hydroxide as a Gastric Antacid, J. Lab. & Clin. Med. **14**:610-614, 1929.

the salts produce in the stomach stops digestion and removes the antiseptic quality of acid chyme.[40]

Calcium carbonate was named as the "ideal" antacid in 1927.[31c] This salt is insoluble in water, a potential alkali and incapable of eliciting a secondary secretion of acid. It may produce a protective coating on an ulcer and have demulcent properties. Undoubtedly superior in many respects in the field of gastric antacids, it is available in a number of official forms. However, calcium carbonate is not without some properties which may be objectionable. It releases carbon dioxide in the presence of free acid, which, as has been said, may be dangerous. Fecaliths and chalk balls may result from its continued use in large amounts,[41] and constipation is sometimes severe.[6a]

A gel of calcium silicate also has been recommended as a gastric antacid and will be discussed under colloids.

Mucin.—Closely resembling gastric mucus, mucin was recommended as a gastric antacid in 1932;[42] however, even though it combines with more acid than most proteins, its antacid value is limited. The beneficial effects come from its demulcent properties. The preparations are comparatively expensive and have not proved as efficacious as desired.[43]

Hydrogen Peroxide.—The use of hydrogen peroxide as a depressant of gastric acidity has been shown to be unsatisfactory.[44] It may cause hemorrhage from an ulcer, and in effective concentrations it produces too much discomfort. In lesser concentrations it has unpredictable results.

Milk.—The antacid value of milk has perhaps been obscured by emphasis on its excellent food value unaccompanied by the secretagogic effect of meat broths and the like as the reason for its inclusion in the diet in cases of ulcer. Being amphoteric, milk is capable of buffering about its own volume of average gastric contents (0.3 per cent hydrochloric acid) to p_H 4, the point of no free acidity.[26] The amphoteric nature of the milk in the Sippy diet helps to mitigate the alkalizing tendency of the excessive administration of alkaline powders. On the other hand, the milk taken daily on the Sippy regimen would, itself, be able to buffer about 1,200 cc. of normal gastric contents. The fat

40. (*a*) Crohn.[39] (*b*) Guillermin, R.: Hyperchlorhydrie et hydrate d' alumine colloidal, Rev. méd. de la Suisse Rom. **44**:243-246, 1924.

41. Eusterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, p. 286.

42. Fogelson, S. J.: The Treatment of Peptic Ulcer with Gastric Mucin: Preliminary Report, J. A. M. A. **96**:673-675 (Feb. 28) 1931; Peptic Ulcer: Its Treatment with Gastric Mucin, Am. J. Nursing **32**:921-925, 1932.

43. Chace.[19e] Rivers, A. B.: Certain Newer Methods of Treating Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **3**:698-704, 1936.

44. Culmer, C. V.; Atkinson, A. J., and Ivy, A. C.: Hydrogen Peroxide as a Depressant of Gastric Acidity, Am. J. Digest. Dis. & Nutrition **4**:219-223, 1937.

content of a mixture of milk and cream would tend to decrease gastric secretion.[35]

Milk to which is added small amounts of sodium bicarbonate,[45] lime water[34d] or a citrate[35] and alkalinized powdered milk[31b] have been used. Sodium citrate added to milk has an especial advantage in preventing large curds in the stomach by fixing the calcium of milk, which is essential to the curdling process.[35] Elimination of heavy curds reduces trauma to the ulcer. Indeed, milk, alone or with small amounts of antacids, is able to control mild peptic ulcer in many cases. Powdered milk, alkalinized with a Sippy powder containing calcium carbonate and sodium bicarbonate, is claimed[46] to be more effective than the same powder given in the usual manner on the Sippy regimen. The tablet form is an added advantage.

Bismuth Compounds.—The bismuth compounds are useful adjuvants in antacid mixtures but are too inefficient as buffering agents to reduce acids satisfactorily unassisted. The subnitrate is without neutralizing power and may, even in moderate quantities, be toxic if certain bacteria are present in the intestine and cause the formation of nitrite from nitrate. Also, the oxycarbonate and the subgallate have practically no neutralizing power.[26] The slight amount of a bismuth salt which goes into solution exerts a mild astringent and antiseptic effect, and the protective and demulcent actions of these insoluble powders are their greatest virtues in the therapy of peptic ulcer. Objections to them may be made because (*a*) they color the stools (black) and thereby may obscure slight melena or may be a source of worry to the neurotic patient[47] and (*b*) they may be severely constipating and if used in large amounts for extended periods may lead to the deposit of concretions in the intestines.[48]

COLLOIDAL ANTACIDS

A great improvement in the armamentarium of the gastric antacids occurred with the introduction of unabsorbable colloidal substances which are capable of reducing gastric acidity to a desired level.

Colloidal Aluminum Hydroxide.—This substance, a specially prepared, colloidal white powder, insoluble in water, tasteless, neutral and amphoteric, was presented at the French congress of medicine[40b] in 1922 and introduced into this country in 1929.[39] Ordinary commercial powdered aluminum hydroxide does not exhibit the high buffering power

45. Winkelstein, A.: One Hundred and Sixty-Nine Studies in Gastric Secretion During the Night, Am. J. Digest. Dis. & Nutrition **1**:778-782, 1935.

46. Wosika, P. H.: The Control of Gastric Acidity in Peptic Ulcer by Alkalinized Powdered Whole Milk Tablets, Am. J. Digest. Dis. & Nutrition **3**: 419-426, 1936.

47. Loevenhart and Crandall.[31c] Hurst.[35]

48. Sollmann, T.: A Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 968.

of the colloidal form and is not as satisfactory.[49] The medicinal powder is used in doses of 1 or 2 Gm. (15 to 30 grains), either dissolved in milk or water or compressed into tablets. One gram of the powder is capable of buffering 35 cc. of tenth-normal hydrochloric acid to p_H 4 in two hours.

The first liquid preparation of colloidal aluminum hydroxide to be reported in this country appeared in 1931,[49] a slightly astringent, gelatinous, white fluid hydrate, with a not unpleasant taste, usually flavored with peppermint. The dose is 4 to 16 cc. (1 to 4 drachms) and each cubic centimeter is capable of buffering 15 to 16 cc. of tenth-normal hydrochloric acid to p_H 4 in four hours. On a basis of dry weight the aluminum hydroxide cream has the advantage of much greater buffering power, presumably because of the greater stability of the colloidal state when the preparation is not dried. Further advantages are: (*a*) The diluted cream may be continuously dripped into the stomach,[50] which is specially advantageous for control of acidity in severe conditions and for the control of acidity at night, which is so often neglected:[45] (*b*) the gel is more easily administered; (*c*) it is more highly adsorbent.[51] Tablets of the powder, however, provide a convenient means of carrying the antacid on the person for relief of distress in emergencies.

Early reports[52] were so enthusiastic over the relief of hyperacidity afforded by colloidal aluminum hydroxide that a healthy skepticism of its merits ensued. Further investigations and experiences with it have now established the fact, fifteen years after its introduction, that it produces remarkable symptomatic relief from pain, nausea and vomiting, even in long-standing and severe conditions, and that relief is almost immediate.[53]

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49. Einsel, I. H., and Rowland, V. C.: The Aluminum Hydroxide Treatment of Peptic Ulcer, Ohio State M. J. **28**:173-174, 1932.

50. (*a*) Dimmel, H.: Ueber Neutralon, Wien. klin. Wchnschr. **39**:1219-1220, 1926. (*b*) Woldman, E. E., and Rowland, V. C.: A New Technique for the Continuous Control of Acidity in Peptic Ulcer by Aluminum Hydroxide Drip, Am. J. Digest. Dis. & Nutrition **2**:733-736, 1936.

51. Woldman, E. E., and Rowland, V. C.: Continuous Acid Adsorption by Aluminum Hydroxide Drip in the Treatment of Peptic Ulcer, Rev. Gastroenterol. **3**:27-35, 1936.

52. (*a*) Guillermin.[40b] (*b*) Swalm, W. A.: Aluminum Silicate (Kaolin) with Aluminum Hydroxide in Certain Intestinal Disorders, M. Rec. **140**:26-31 and 68-76, 1934.

53. (*a*) Crohn.[39] (*b*) Einsel and Rowland.[49] (*c*) Woldman and Rowland (footnotes 50 *b* and 51). (*d*) Heilpern, L.: Alucol Therapy of Hyperacidity, Polska gaz. lek. **11**:349-352, 1932. (*e*) Einsel, I. H.; Adams, W. L., and Myers, V. C.: Aluminum Hydroxide in the Treatment of Peptic Ulcer, Am. J. Digest.

(Footnote continued on next page)

The percentage of poor results with colloidal aluminum hydroxide is 8.1 in the largest series (125 cases) for which figures are given.[53e] In another instance only 1 patient of 24 receiving this treatment showed poor results.[53g] Other reports show almost universal symptomatic relief. The unusual success obtained with this antacid is due, in part, to the ready cooperation of the patients, who find the results so satisfactory and the routine of treatment so acceptable that they are unwilling to use other antacids. Hospitalization is unnecessary in many cases in which it would ordinarily be indicated, because of the quick recovery with the use of colloidal aluminum hydroxide. It is significant that no adverse reports on the use of this antacid have appeared.

The mechanism of action of colloidal aluminum hydroxide is multiple, and the importance of each part in producing the therapeutic result is difficult to evaluate. Its slight astringent and its demulcent property undoubtedly play a part. It is reported [54] that flaky curds, presumably precipitated mucus, covering the folds of the gastric and the duodenal mucosa, are found at autopsy when animals are killed after receiving the preparation in large doses for a time. This protective action probably accounts for some of the good effects seen with therapeutic doses, since a preparation of aluminum hydroxide with low buffering power was not devoid of good effects.[49]

The colloidal forms, however, have considerable buffering power, and the buffering of free acid plays an important role in obtaining the more satisfactory results seen when they are used.[53f] The physicochemical properties of the colloid cause an adsorption of hydrochloric acid, which is characterized by an immediate rapid decrease in the functional acidity of the gastric juice, with a more gradual reduction continuing. The p_H cannot go beyond neutrality, and usually the increase is to approximately p_H 4. Thus digestion may not be entirely stopped and a slight acidity, not sufficient to cause acid corrosion, exerts some antiseptic influence. Some reaction between the aluminum hydroxide and the hydrochloric acid takes place, with formation of aluminum chloride. In an alkaline intestine aluminum hydroxide is reprecipitated and the chloride reabsorbed. It is unlikely that the hydrochloric acid adsorbed by the colloid is excreted in the feces to any great extent, as Kreis stated [33] otherwise the mineral constituents of the blood would probably be disturbed. That the latter occurs has been disproved.[53f]

The colloid probably exerts also an adsorptive action on toxins (histamine and the like in intestinal putrefaction), on gases and on

Dis. & Nutrition **1**:513-516, 1934. (*f*) Adams, W. L.; Einsel, I. H., and Myers, V. C.: Aluminum Hydroxide as an Antacid in Peptic Ulcer, ibid. **3**:112-120, 1936. (*g*) Jones, C.: Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer, ibid. **4**:99-102, 1937.

54. Ivy, A. C.; Terry, T.; Fauley, G. B., and Bradley, W. B.: The Effect of Administration of Aluminum Preparations on the Secretory Activity and Gastric Acidity of the Normal Stomach, Am. J. Digest. Dis. & Nutrition **3**:879-883, 1937.

bacteria, removing them from the ulcerated areas and from the intestine. This is strongly indicated by the particularly good results obtained in the treatment of intestinal disturbances, probably by the strong adsorptive power of colloidal aluminum hydroxide.[55]

Concerning the mechanism of action of this antacid, it is highly significant that evidence is at hand to indicate that it combats three major factors in the causation of peptic ulcer, namely: (*a*) trauma, by its protective and demulcent properties; (*b*) acid corrosion, by its antacid effect; (*c*) infection, by its adsorptive action on toxins and bacteria.

Toxic local effects which might be anticipated, since colloidal aluminum hydroxide is used as a protein precipitant, have been proved absent.[56] Systemic poisoning by aluminum and disturbance of the acid-base equilibrium also have been ruled out.[57] Further, the alkaline reaction of the intestine peptizes the aluminum hydroxide to a more stable gel with the absorption of more water, so that intestinal concretions are unlikely.[52b] Concretions have never been reported as a complication when aluminum hydroxide was used.

Direct evidence of the therapeutic value of colloidal aluminum hydroxide, in addition to the symptomatic relief already mentioned, is the rapid disappearance of the ulcer, as shown by fluoroscopic or roentgen examination, in an average of thirty days after its administration is begun.[53g] Recurrence of symptoms and relapses are relatively less frequent, but it must be remembered that there is no evidence that this or any other antacid affects the tendency to recurrence in patients with the ulcerative diathesis if care and discretion in the diet and habits are abandoned.

On the basis of its merits and freedom from the undesirable qualities of most antacids, it seems justified to repeat the statement, "it appears that colloidal aluminum hydroxide is the most satisfactory antacid thus far employed,"[53f] and to add that slight constipation, which is easily controlled, is the only objection to the use of colloidal aluminum hydroxide which has been mentioned. The constipation usually occurs only with large doses. Five or six preparations are now on the market, and the cost of medication is less than when Sippy powders are used.

55. Swalm.[52b] Fradkin, W. Z.: The Control of Rectal Bleeding in the Convalescent Ulcerative Colitis Patient, J. Lab. & Clin. Med. **22**:896-899, 1937.

56. Adams, Einsel and Myers.[53f] Ivy, Terry, Fauley and Bradley.[54] Beazell, J. M.; Schmidt, C. R., and Ivy, A. C.: The Effect of Aluminum Hydroxide Cream on Absorption from the Gastro-Intestinal Tract, Am. J. Digest. Dis. **5**: 164-165, 1938.

57. Adams, Einsel and Myers.[53f] Ivy, Terry, Fauley and Bradley.[54]

Substances Used Perorally to Lower Gastric Hyperacidity, with Some of the Data Useful in Rationally Choosing Among Them

Substance	Soluble in Water	Release of Gas	Adsorptive Power: High	Adsorptive Power: Low	Acid-Neutralizing Power: High	Acid-Neutralizing Power: Medium	Acid-Neutralizing Power: Low	Acid-Neutralizing Power: Absent	Antacid Action: Systemic	Antacid Action: Local Only	"Rebound" Secretion of Acid	Effect on Urine: Alkalinizes	Effect on Urine: Acidifies	Action on Bowels: Constipating	Action on Bowels: Laxative	Local Protective Action	Formation of Concretions	Production of Toxic Effects
Aluminum hydroxide, colloidal	..	..	+	..	+	..	..	..	..	+	..	..	..	+	..	+	..	..
Aluminum silicate	..	..	..	..	..	..	..	+	..	..	..	..	..	+	..	+	..	..
Bismuth subcarbonate U. S. P.	..	+	..	..	..	..	..	+	..	..	..	..	..	+	..	+	+	..
Bismuth subgallate U. S. P.	..	..	..	..	..	..	..	+	..	..	..	..	..	+	..	+	+	..
Bismuth subnitrate U. S. P.	..	..	..	..	..	..	..	+	..	..	..	..	..	+	..	+	+	+
Calcium carbonate, precipitated, U. S. P.	..	+	..	..	..	+	..	..	..	+	+	..	+	+	..	+	+	..
Calcium hydroxide, solution, U. S. P	+	..	..	..	..	..	+	..	..	..	+	..	..	..	+	..	..	..
Calcium phosphate, precipitated, N. F.	..	..	..	..	..	+	..	..	..	+	..	..	..	+	..	..	..	..
Hydrogen peroxide, solution, U. S. P.	+	+	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	+
Magnesium carbonate U. S. P.	..	+	..	+	..	..	..	..	..	+	+	..	..	..	+	..	..	+
Magnesia magma U. S. P.	..	..	..	..	..	..	..	+	..	+	..	..	..	..	+	..	..	+
Magnesium oxide, heavy, U. S. P.	..	..	..	..	+	..	..	..	..	+	+	..	..	..	+	..	..	+
Magnesium peroxide	..	+	..	..	+	..	..	..	..	+	+	..	..	..	+	..	..	+
Magnesium phosphate, tribasic	..	..	..	..	..	+	..	..	..	+	..	..	..	..	+	..	..	..
Magnesium trisilicate, synthetic	..	..	+	..	+	..	..	..	..	+	..	..	..	+	..	+	..	..
Milk (whole, sweet)	..	..	..	..	..	..	+	..	..	+	..	..	..	..	..	..	..	..
Potassium acetate U. S. P.	+	..	..	..	..	..	+	..	+	..	+	+	..	..	+	..	..	+
Potassium bicarbonate U. S. P.	+	+	..	..	+	..	..	..	+	..	+	+	..	..	+	..	..	+
Potassium citrate U. S. P.	+	..	..	..	..	+	..	..	+	.	..	+	..	..	+	..	..	+
Sodium acetate U. S. P.	+	..	..	..	..	+	..	..	+	..	..	+	..	..	+	..	..	+
Sodium bicarbonate U. S. P.	+	+	..	..	+	..	..	..	+	..	+	+	..	..	+	..	..	+
Sodium citrate U. S. P.	+	..	..	..	..	+	..	..	+	..	..	+	..	..	+	..	..	+
Sodium hydroxide (dilute solution)	+	..	..	..	+	..	..	..	+	..	+	+	..	..	+	..	..	+
Mineral waters	+	+	..	..	..	..	+	..	..	..	..	+	..	..	+	..	..	+

Other Colloidal Substances.—Colloidal barium sulfate,[58] bismuth silicate [59] and calcium silicate [60] also have been suggested for use as gastric antacids. In general, they have not received enough attention to allow adequate judgment of their value.

Magnesium Trisilicate.—Recently a synthetic hydrated trisilicate of magnesium [61] with adsorbent properties far superior to those of natural silicates has been introduced, and because of its unusual nature, it deserves more attention. It is a white, tasteless, insoluble powder, which reacts slowly with hydrochloric acid. One gram reacts with 155 cc. of tenth-normal hydrochloric acid in four hours, the neutralization occurring rapidly at first and becoming slower as the reaction proceeds. Magnesium trisilicate is stated to react with hydrochloric acid in the stomach according to the following equation:

$$Mg_2Si_3O_8.nH_2O + 4\ HCl = 2\ MgCl_2 + 3\ SiO_2 + (n+2)\ H_2O$$

The silicon dioxide produced by this reaction is a hydrated gel without antacid properties, but it enters the duodenum and exerts a high adsorptive effect on toxins, bacteria and the like. The gel is thought to be a factor in producing a slower, more prolonged neutralization of acid, because it retards the diffusion of acid. Although its antipeptic, antacid and antitoxic properties seem to have been well studied,[61] the possibility of its producing a secondary acid rebound has not been ruled out yet, nor are studies of its toxicity complete and confirmed. In the single report of its use made since its introduction in 1936,[62] the results were said to be good.

SUMMARY

The various antacids which are used in the treatment of gastric hyperacidity and peptic ulcer are discussed from a pharmacologic point of view and much of the data which are of value in making a choice among them tabulated. The advantages and disadvantages of each are considered, and their pharmacologic actions, as shown by researches and clinical experiences, are used as a basis for evaluating the best antacids available at the present time.

58. Finkelstein, J.: Colloidal Barium Sulfate in Hyperchlorhydric Gastritis, Strasbourg méd. **96**:429-432 and 465-473, 1936.

59. Bonanno, A. M.: Bismoterran (Bismuth Silicate Preparation) Therapy, Minerva med. **1**:812-814, 1934.

60. Becher, E.: Beobachtungen über Gastro-Sil, ein neues Mittel zur Behandlung der Hyperazidität, Med. Klin. **29**:20-21, 1933. Frisch, J.: Beitrag zur Therapie der aciden Magenerkrankungen, Wien. med. Wchnschr. **84**:1404-1406, 1934.

61. Mutch, N.: The Silicates of Magnesium, Brit. M. J. **1**:143-148, 205-208 and 254-257, 1936.

62. Mann, W. N.: Experiments on the Neutralization of HCl by Magnesium Trisilicate, Guy's Hosp. Rep. **87**:151-157, 1937.

CHANGES IN THE ACID-BASE BALANCE DURING ALKALI TREATMENT FOR PEPTIC ULCER

A CLINICAL ANALYSIS OF ALKALOSIS IN TWENTY-EIGHT PATIENTS

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This paper presents biochemical and clinical studies on patients receiving alkali therapy for peptic ulcer, as well as an analysis of the clinical records of 28 patients in whom alkalosis developed during treatment for ulcer.

Sippy [1] introduced the practice of using large daily doses of alkali powders for the treatment of peptic ulcer in 1915. He observed toxic symptoms in some of his patients (Gatewood and associates [2]). In 1923 Hardt and Rivers [3] published the first detailed account of alkali intoxication arising during the course of the Sippy treatment. They named the condition "alkalosis." Since that time cases of alkalosis have been reported with increasing frequency, so that the condition is now recognized as an important complication of the treatment of peptic ulcer (Hurst and Stewart [4]; Jordan and Kiefer [5]; Cooke [6]; Berger and Binger [7]; Oakley,[8] and others). In the majority of patients who receive the Sippy type of treatment symptoms of alkalosis do not, however, develop.

From the Department of Medicine, University of Chicago.

1. Sippy, B. W.: Gastric and Duodenal Ulcer: Medical Cure by an Efficient Removal of Gastric Juice Corrosion, J. A. M. A. **64**:1625 (May 15) 1915.

2. Gatewood, W. E.; Gaebler, O. H.; Muntwyler, E., and Myers, V. C.: Alkalosis in Patients with Peptic Ulcer, Arch. Int. Med. **42**:79 (July) 1928.

3. Hardt, L. J., and Rivers, A. B.: Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, Arch. Int. Med. **31**:171 (Feb.) 1923.

4. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, London, Oxford University Press, 1929, p. 399.

5. Jordan, S. M., and Kiefer, F. D.: Factors Influencing Prognosis in the Medical Treatment of Duodenal Ulcer, Am. J. Surg. **15**:472 (March) 1932.

6. Cooke, A. M.: Alkalosis Occurring in the Alkaline Treatment of Peptic Ulcers, Quart. J. Med. **1**:527 (Oct.) 1932.

7. Berger, E. H., and Binger, M. W.: The Status of the Kidneys in Alkalosis, J. A. M. A. **104**:1383 (April 20) 1935.

8. Oakley, W.: Alkalosis Arising in Treatment of Peptic Ulcer, Lancet **2**: 187 (July 27) 1935.

Several theories have been proposed to account for the intolerance to alkalis occasionally encountered in certain persons. It was early recognized that in patients with renal disease alkalis are poorly tolerated, and alkalosis develops readily (Hardt and Rivers [3]). This observation has been confirmed by many investigators. High grade pyloric obstruction causing the loss of large amounts of gastric juice has been recognized as a cause of alkalosis by several observers (Brown and co-workers [9]; Gatewood and co-workers [2]; Hurst and Stewart [4]; Oakley [8]; Jeghers and Lerner,[10] and others). In fact, the loss of hydrochloric acid in pyloric obstruction may cause alkalosis when no alkalis have been administered (Grant [11]; Brown and co-workers [9]; Houghton and co-workers [12]; McArthur and Payne [13]; Pfeiffer [14]; Butler,[15] and others). This has been shown experimentally also, by MacCallum and co-workers.[16] Hemorrhage was recognized as a contributory cause of alkalosis by Jordan and Kiefer,[5] Berger and Binger,[7] Jeghers and Lerner [10] and others. Hepatic disease may be an etiologic factor according to Eusterman and Balfour.[17] Berger and Binger [7] expressed concurrence in this view. Kin [18] and MacNider [19] have shown experimentally that the

9. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction: Renal Insufficiency Complicating Gastric Tetany, Arch. Int. Med. **32**:425 (Sept.) 1923.

10. Jeghers, H., and Lerner, H. H.: Syndrome of Alkalosis Complicating Treatment of Peptic Ulcer: Report of Cases with Review of Pathogenesis, Clinical Aspects and Treatment, New England J. Med. **214**:1236 (June 18) 1936.

11. Grant, S. B.: Tetany: A Report of Cases with Acid-Base Disturbance, Arch. Int. Med. **30**:355 (Sept.) 1922.

12. Houghton, L. W.; Venables, J. F., and Lloyd, N. L.: Toxemia Following Obstruction Near Pylorus, Guy's Hosp. Rep. **75**:149 (April) 1925.

13. McArthur, C. B., and Payne, W. W.: Alkalosis in Congenital Hypertrophic Stenosis, Lancet **1**:286 (March 5) 1930.

14. Pfeiffer, D. B.: Alkalosis Due to Pyloric Stenosis Simulating Nephritic Uremia, Ann. Surg. **92**:900 (Nov.) 1930.

15. Butler, A. M.: Acidosis or Alkalosis in Infants and Children with Gastrointestinal Disturbances, Chronic Nephritis, and Diabetes Mellitus, M. Clin. North America **18**:1205 (Jan.) 1935.

16. MacCallum, W. G.; Lintz, J.; Vremilye, H. N.; Leggett, T. H., and Boas, E.: The Effect of Pyloric Obstruction in Relation to Gastric Tetany, Bull. Johns Hopkins Hosp. **31**:1 (Jan.) 1920.

17. Eusterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, p. 288.

18. Kin, T.: Ueber die Säure-Basengleichgewicht regulierende Funktion der Leber, J. Chosen M. A. **22**:1 (Jan.) 1932; abstracted, Chem. Abstr. **26**:6002 (Nov. 20) 1932.

19. MacNider, W. deB.: The Influence of Liver Degeneration and Recuperation on the Acid-Base Equilibrium of the Blood, J. Pharmacol. & Exper. Therap. **50**:108 (Jan.) 1934.

liver has an important role in maintaining the acid-base balance of the body. Sensitivity to alkali as a cause of alkalosis was suggested by Rafsky and his co-workers.[20] They recommended that small doses be used at the onset of treatment, followed by gradually increasing doses, with special precautions for patients with a history of allergy.

ACID-BASE BALANCE

The biochemical literature on the subject of acid-base balance is extensive and diffuse, and it is not generally available to the clinician. As a certain knowledge of this field is necessary for the evaluation of the acid-base disturbances encountered in patients and for the interpretation of the data presented in this paper, a brief review of the biochemical background is presented.

The term "acid-base balance" may be defined as the equilibrium between the anions and the cations in the body. More commonly, the term refers to that equilibrium in the blood, for the acid-base balance of the blood reflects that of the body. Although numerous kinds of ions are involved in this balance, a picture of it that is adequate for most purposes will be given by the determination of two characteristics of the blood: the p_H and the carbon dioxide content. The latter is made up of two components, the serum bicarbonate, $BHCO_3$, and the carbonic acid, H_2CO_3. These can be calculated from the values of p_H and carbon dioxide content by means of the Henderson-Hasselbalch equation:

$$p_H = pK' + \log \frac{BHCO_3}{H_2CO_3}.$$

In this equation pK′ is the negative logarithm of K′, which is the apparent dissociation constant for carbonic acid. The pK′ for human serum is 6.10 at 38 C.[21] The carbonic acid component may be expressed conveniently as the partial carbon dioxide tension of the blood, pCO_2, measured in terms of millimeters of mercury. This may be done by applying an appropriate factor which includes the solubility coefficient of carbon dioxide in blood serum.

Although a knowledge of the three values—those of p_H, of serum bicarbonate and of partial carbon dioxide tension—is necessary for a full characterization of the acid-base balance, that of serum bicarbonate is the most informative single value. It frequently is called the "alkali reserve," because it closely mirrors the amount of available alkali in the entire body.

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20. Rafsky, H. A.; Schwartz, J., and Kruger, A. W.: The Relation of Alkalosis to Peptic Ulcer, J. A. M. A. **99**:1582 (Nov. 5) 1932.

21. Hastings, A. B.; Sendroy, J., Jr., and Van Slyke, D. D.: Studies of Gas and Electrolyte Equilibria in Blood: XII. The Value of pK′ in the Henderson-Hasselbalch Equation for Blood Serum, J. Biol. Chem. **79**:183 (Sept.) 1928.

Acidosis and Alkalosis.—The disturbances of acid-base balance encountered in patients may be (1) respiratory or (2) metabolic in origin.

1. The respiratory changes are characterized chiefly by an increase or a decrease of the carbonic acid, due to abnormalities of respiratory activity. These changes may be (*a*) an excess of carbon dioxide (respiratory acidosis) due to underventilation or (*b*) a deficit of carbon dioxide (respiratory alkalosis) due to hyperventilation.

2. The metabolic changes are caused chiefly by an increase or a decrease of the available alkali of the body. These changes may be (*a*) an excess of acid (metabolic acidosis) due to the addition of fixed acid to the body or the loss of alkali or (*b*) an excess of alkali (metabolic alkalosis) due to the addition of alkali or the loss of fixed acid from the body.

TABLE 1.—*Changes in the Components of the Acid-Base Balance Occurring in Various Kinds of Acidosis and Alkalosis*

Condition	Cause	p_H	Bicarbonate	Carbonic Acid
Respiratory alkalosis (CO_2 deficit)	Hyperventilation	Increased	Slightly decreased	Decreased
Respiratory acidosis (CO_2 excess)	Underventilation	Decreased	Slightly increased	Increased
Metabolic alkalosis (alkali excess)	Addition of alkali or loss of fixed acid	Increased	Increased	Slightly increased
Metabolic acidosis (alkali deficit)	Addition of fixed acid or loss of alkali	Decreased	Decreased	Slightly decreased

The changes occurring in the acid-base balance in these conditions are presented in table 1. In addition to the four simple conditions, combinations may occur.

Interpretation of Acid-Base Changes by Triaxial Graphing.—The nature of clinical disturbances of the acid-base balance may be readily understood when the disturbances are represented as pathways, which denote not only the degree but also the direction of displacement of the acid-base balance. These pathways may be constructed by plotting the acid-base data on triaxial graph paper [22] as described by Hastings and

22. Triaxial graph paper, on which the coordinates are equally spaced at 60 degree angles, is adapted for plotting data which are related according to the equation $ax + by + cz = K$. The Henderson-Hasselbalch equation,

$$p_H = pK' + \log \frac{BHCO_3}{H_2CO_3}$$

is suited for such graphing when it is placed in the form

$$p_H - \log BHCO_3 + \log H_2CO_3 = pK'.$$

Log pCO_2 may be substituted for log H_2CO_3 by including an appropriate factor.

Steinhaus.[23] Chart 1 presents data on the acid-base balance for 2 patients graphed by this method. It will be seen that any given point on the graph indicates the values of p_H, of serum bicarbonate and of partial carbon dioxide tension. The four major types of acid-base disturbance are shown as pathways, their positions having been determined empirically by clinical and experimental observations. One may thus readily evaluate the roles of respiratory and metabolic factors in producing any given disturbance of acid-base balance.

Values Needed to Evaluate Disturbances of Acid-Base Balance.—It is common practice in evaluation of disturbances of the acid-base balance to determine the carbon dioxide content only. This value alone is not adequate, for, as has been stated, without the value for the p_H also, the carbon dioxide content cannot be separated into its two components, serum bicarbonate and partial carbon dioxide tension. From

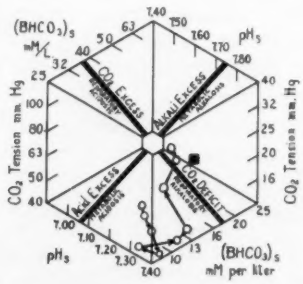

Chart 1.—Triaxial graphing of data on the acid-base balance. Any given point indicates the appropriate values of p_H, serum bicarbonate and partial carbon dioxide tension. The position of the three sets of coordinates may be understood by referring to the figures of a clock. The constant p_H lines run in the direction of 6 and 12 o'clock; the constant serum bicarbonate lines, in the direction of 4 and 10 o'clock, and the constant partial carbon dioxide tension lines, in the direction of 2 and 8 o'clock. The small center hexagon represents the normal range of the acid-base balance. The four major pathways of displacement of the acid-base balance are indicated by heavy lines.

The black square indicates the data for F. S., in whose case the carbon dioxide content was normal (because of a high bicarbonate content in the serum and a low partial carbon dioxide tension counterbalacing one another) but the p_H was greatly elevated. The ten circles indicate data for L. G. for twenty-one days at intervals of one to three days, showing recovery from metabolic acidosis which was complicated by respiratory alkalosis. In the first five determinations, the p_H was normal, although the carbon dioxide content was low (made up of a low bicarbonate content in the serum and a low partial carbon dioxide tension).

23. Hastings, A. B., and Steinhaus, A. H.: A New Chart for the Interpretation of Acid-Base Changes and Its Application to Exercise, Am. J. Physiol. **96**: 538 (March) 1931.

the foregoing paragraphs it will be seen that the direction of displacement of the acid-base balance cannot be evaluated without these values.

The inadequacy of determining either the carbon dioxide content or the p_H alone will be further appreciated when it is realized that serious disturbances of the acid-base balance may occur in which one or the other of these values remains normal.

For example, in F. S. (chart 1), a 70 year old woman, a disturbance occurred during alkali therapy, and the acid-base balance was displaced between the pathway of metabolic alkalosis and that of respiratory alkalosis so that an increased serum bicarbonate and a decreased partial carbon dioxide tension counterbalanced one another. The carbon dioxide content thereby remained normal (25.5 millimols per liter), but the p_H was markedly elevated (p_H 7.59).

As a contrasting example, the following observations were made on L. G., a 57 year old white woman who had impaired renal function. She was given ammonium chloride in the treatment of a urinary infection, and high grade metabolic acidosis developed in combination with respiratory alkalosis due to hyperventilation. This resulted in markedly decreased concentrations of serum bicarbonate and carbonic acid and therefore in an exceedingly low carbon dioxide content of the blood, but the p_H remained normal, namely, p_H 7.40.[24] The results of ten determinations of the acid-base balance, made on L. G. over a period of twenty-one days, are presented in chart 1.

The determination of serum chlorides is frequently desirable in studies of alkalosis, but it is not considered an essential procedure. A decrease of the serum chlorides has frequently been observed to accompany the increased carbon dioxide content in alkalosis, regardless of the cause. This effect depends on the fact that the total base concentration of the serum usually is maintained at a relatively constant level. The total base is combined, for the most part, with Cl^- and HCO_3^- ions. Consequently, a change in the concentration of one of these cations causes a compensatory and inverse alteration in the concentration of the other. Thereby, a normal electrolyte content and a normal osmotic pressure are preserved. This relation is illustrated by data on S.K. (no. 25 in the alkalosis series) in chart 2. It will be seen that the curves of the serum bicarbonate and of the serum chlorides are nearly mirror images of one another. Essentially the same picture may be produced by a loss of hydrochloric acid in pyloric obstruction, but here there is a compensatory rise of the bicarbonate content of the serum, which is derived from the ubiquitous carbonic acid. Exceptions to this complementary relation of the Cl^- and HCO_3^- may occur, as in the rare instances when the total base of the plasma is altered or when the anions of other acids enter the blood.

24. This case is being reported in full elsewhere.

DAILY VARIATIONS IN THE ACID-BASE BALANCE DURING ALKALI THERAPY FOR PEPTIC ULCER

A. Material.—Determinations of the acid-base balance were made on cutaneous blood twice daily in 16 cases. The observations were commenced the day before the onset of a modified Sippy treatment and were continued morning and evening for a variable number of days, usually seven to fourteen. As nearly as possible, the daily dose of alkali powders was kept constant. Powders consisting of 2 Gm. of sodium bicarbonate and 0.6 Gm. of calcium carbonate were given every hour from 8:30 a. m. to 6:30 p. m. and every half hour from 7 to 9 p. m. Thus, sixteen powders were given daily, providing 32 Gm. of sodium bicarbonate and 9.6 Gm. of calcium carbonate. Ninety cubic centimeters of a mixture of milk and cream was given every hour from 7 a. m. to 7 p. m. In some instances three small bland feedings also were given. Any variations from this schedule

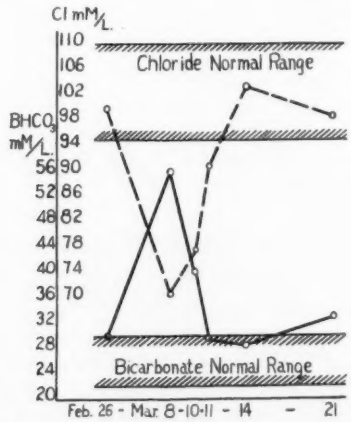

Chart 2 (patient 25 in the alkalosis series).—The inverse relation of serum bicarbonate and serum chlorides, in alkalosis.

will be noted. Samples of blood for determinations of the acid-base balance were obtained at 8:30 a. m. and at 9:30 p. m.

The daily fluid intake and urinary output and the bicarbonate content and specific gravity of the twenty-four hour specimens of urine were determined on 2 patients. For each of these patients a three day period of restricted fluid intake was observed. Limitation of fluid intake could not be enforced to extreme degrees, because administration of the sixteen daily powders was continued, and water was necessary to swallow them. The hourly administration of the mixture of milk and cream was discontinued.

B. Methods.—The microtechnic of Shock and Hastings [25] was used for determinations of the acid-base balance, for with this method venipuncture is not

25. Shock, N. W., and Hastings, A. B.: Studies of the Acid-Base Balance of the Blood: I. A Microtechnique for the Determination of the Acid-Base Balance of the Blood, J. Biol. Chem. **104**:565 (March) 1934.

necessary. A 0.1 cc. sample of whole blood taken from the finger tip under oil was used to determine the percentage of erythrocytes by means of the hematocrit, the p_H colorimetrically by the method of Hastings and Sendroy [26] and the carbon dioxide content of the whole blood by the method of Van Slyke and Neill.[27] Determinations were usually made in triplicate. From these experimental data the bicarbonate content of the serum and the partial carbon dioxide tension were calculated with the nomographic chart designed for this purpose by Hastings and Shock.[28]

Cutaneous blood closely approximates arterial blood in composition.[29] Saito [30] has shown that cutaneous blood can be used as well as venous blood for following the acid-base changes in cases of acidosis or of alkalosis. The normal range for the acid-base balance of cutaneous blood is p_H 7.35 to 7.47, serum bicarbonate 23 to 30 millimols per liter and partial carbon dioxide tension 40 to 50 mm. of mercury (Shock and Hastings [31]).

C. Results.—Data for 3 patients, which are considered characteristic of the group, are presented in chart 3. With 1 exception all patients studied remained free from symptoms of alkalosis, not only during the periods of intensive biochemical observation but also during their subsequent observation in the hospital and the outpatient clinic. In all cases there was a shift of the acid-base balance toward the alkaline side. There was usually an elevation of the p_H to 7.50 to 7.54 and an elevation of the serum bicarbonate to 36 to 38 millimols per liter. Thus, it may be said that all patients receiving the Sippy type of therapy have some degree of chemical alkalosis, although clinical alkalosis seldom develops.

A distinct tolerance to alkali developed in most patients. Usually the greatest displacement of the acid-base balance occurred on the evening of the third day of treatment. A few patients reached the peak on the evening of the second day. Thereafter, the daily displacement of the acid-base balance, especially of the bicarbonate content of

26. Hastings, A. B., and Sendroy, J., Jr.: Studies of Acidosis: Colorimetric Determination of Blood p_H at Body Temperature Without Buffer Standards, J. Biol. Chem. **61**:695 (Oct.) 1924.

27. Van Slyke, D. D., and Neill, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523 (Sept.) 1924.

28. Hastings, A. B., and Shock, N. W.: Studies of the Acid-Base Balance of the Blood: II. A Nomogram for Calculation of Acid-Base Data for Blood, J. Biol. Chem. **104**:575 (March) 1934.

29. Lundsgaard, C., and Møller, E.: Investigations on the Oxygen Content of Cutaneous Blood (So-Called Capillary Blood), J. Exper. Med. **36**:559 (Nov.) 1922.

30. Saito, K.: Gaseous Content of Arterial, Cutaneous and Venous Blood in Normal State, Acidosis, and Alkalosis, J. Biol. Chem. **25**:89 (Jan.) 1937.

31. Shock, N. W., and Hastings, A. B.: Studies of the Acid-Base Balance of the Blood: III. Variation in the Acid-Base Balance of the Blood in Normal Individuals, J. Biol. Chem. **104**:585 (March) 1934.

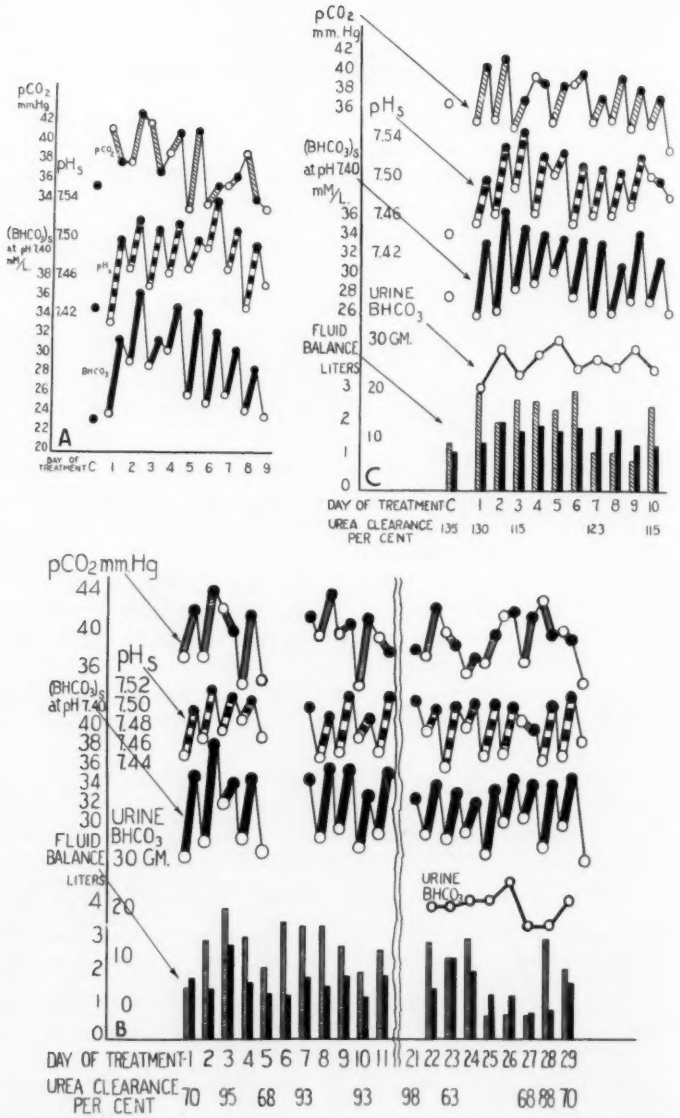

Chart 3.—*A* (D. S.), data on the acid-base balance determined twice daily, demonstrating the development of a tolerance to alkalis during daily ingestion of sixteen powders (32 Gm. of sodium bicarbonate and 9.6 Gm. of calcium carbonate). The open-faced circles indicate morning determinations; the solid circles indicate evening determinations. The heavy bars denote the shift occurring during the day period of ingestion of powder; the light lines denote the degree of recovery during the night. *B* (M. S.), data on the acid-base balance determined twice daily, as in chart 3 *A*. The fluid intake is indicated by shaded columns; the urinary output, by solid columns. Sixteen alkaline powders were taken daily (32 Gm. of sodium bicarbonate and 9.6 Gm. calcium carbonate). *C* (D. W.), data on the acid-base balance determined twice daily, demonstrating the development of tolerance to alkalis.

the serum, tends to decrease. This trend is best seen in the case of D. S. (chart 3*A*). In the case of M. S. (chart 3*B*), the acid-base balance was determined twice daily during thirty days of treatment. (Chemical observations were interrupted twice, but the daily ingestion of alkali remained constant.) The peak of the acid-base displacement occurred on the evening of the third day. D. W. (chart 3*C*) reached the peak on the second day.

The daily excretion of bicarbonate in the urine was found to vary from 17 to 27 Gm. for M. S. (chart 3*B*) and from 20 to 31 Gm. for D. W. (chart 3*C*). Excretion of bicarbonate was maintained during the three day periods of restriction of fluid intake, for, although the volume of urine was decreased, the urine became more concentrated. These data, together with the data for fluid intake and urinary output,

TABLE 2.—*Effect of Limitation of Fluid Intake on Urinary Excretion of Bicarbonate*

	24 Hour Fluid Intake, Cc.	24 Hour Specimen of Urine		
		Volume, Cc.	Specific Gravity	Bicarbonate Content, Gm.
I. M. S. (chart 3*A*)				
(*a*) Daily average when water was taken as desired	2,580	1,790	1.020	21.5
(*b*) Daily average when fluid was restricted for a 3 day period	758	1,240	1.026	22.4
II. D. W. (chart 3*B*)				
(*a*) Daily average when water was taken as desired	2,670	1,700	1.020	26.1
(*b*) Daily average when fluid was restricted for a 3 day period	1,120	1,538	1.025	27.6

are summarized in table 2. With the exception of the periods of restriction, the average daily fluid intake and output were somewhat greater than normal. During the periods of restriction the volume of urine exceeded the fluid intake. Except for great thirst, no symptoms were noted during these periods.

DAILY VARIATION OF THE ACID-BASE BALANCE DURING THE DEVELOPMENT OF CLINICAL ALKALOSIS

In 1 of the patients studied, clinical alkalosis developed during the period of observation.

C. B., a 43 year old white man, had been receiving a modification of the treatment for ambulatory patients with ulcer, including small doses of alkali, for six months. As the ulcer had not healed, he was hospitalized for intensive alkali therapy. The acid-base balance was determined twice daily from the day the alkali therapy was started until recovery from the ensuing alkalosis had occurred. The data are presented graphically in chart 4.

On the evening of the third day of treatment, the bicarbonate content of the serum had reached 46.5 millimols per liter, and the p_H was 7.68. This was a far greater degree of chemical alkalosis than was seen in the other patients studied (chart 3). Although this was the greatest displacement of the acid-base balance observed in this patient, the onset of symptoms did not occur until the following (fourth) day, and symptoms were not marked until the fifth day. On the fourth day symptoms were vague and unobtrusive, namely, a distaste for powders and for milk and cream. It so happened that on this day only nine of the usual sixteen powders were taken, because a fluoroscopic examination of the stomach had been

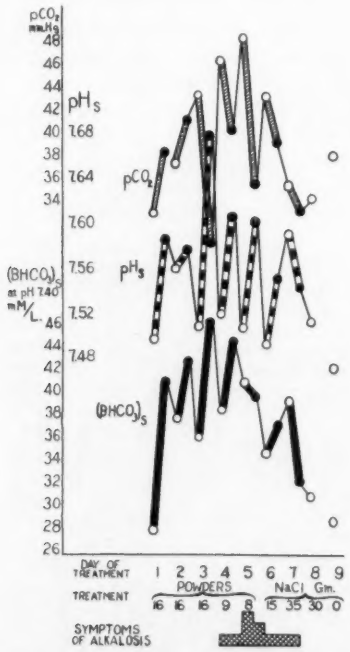

Chart 4 (C. B.).—Data on the acid-base balance determined twice daily during development of and recovery from clinical alkalosis. Note that the symptoms were not correlated with the degree of chemical alkalosis.

scheduled and the patient fasted until 3 p. m. Severe symptoms developed during the afternoon of the fifth day—headache, lassitude, nausea and vomiting, in addition to a continuation of the distaste for powders and for milk and cream. Administration of powders was discontinued at 4 p. m., eight powders having been taken. In spite of the more severe symptoms on the fifth day, the acid-base balance was less disturbed than on the two previous days.

A slow, continuous infusion of a mixture of milk and cream through an indwelling stomach tube was started on the sixth day. Five grams of sodium chloride was added to each liter of the mixture. At the end of the second day

of this treatment (seventh day of treatment for ulcer) all symptoms and chemical evidence of alkalosis had disappeared.

By plotting the data for C. B. triaxially (chart 5) one sees that the direction of the daily displacement of the acid-base balance changed during the development of alkalosis. On the first day of treatment the direction paralleled the pathway of metabolic alkalosis. On the third day the displacement was greatest of all, but its direction had changed so that it ran about midway between the pathway of metabolic alkalosis and that of respiratory alkalosis. On the fifth day, when symptoms were most marked, the direction had changed even more, so that the direction of the day's displacement now paralleled the pathway of respiratory akalosis, although the acid-base balance for the entire day was removed far out along the pathway of metabolic alkalosis. Thus, the direction of

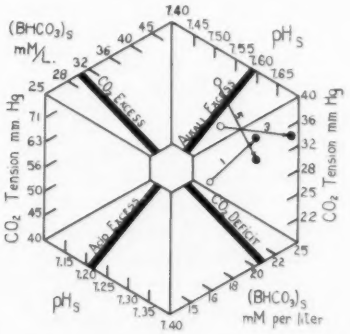

Chart 5 (C. B.).—Triaxial graphing of data on the acid-base balance demonstrating a change in the direction of the daily displacement accompanying the development of clinical alkalosis. The open-faced circles indicate morning analyses; solid circles, evening analyses; the arrows, the direction of the day's displacement, and the numbers above the arrows, the day of treatment.

the fifth day's displacement crossed the pathway of metabolic alkalosis at nearly right angles.

This shift in the direction of displacement is interpreted as a protective mechanism of the body, which prevents the serum bicarbonate from departing too far from normal. The change in direction was due to a deficit of carbon dioxide (or respiratory alkalosis) complicating the metabolic alkalosis and was caused by hyperventilation.

LACK OF CORRELATION BETWEEN CLINICAL AND CHEMICAL ALKALOSIS

The symptoms of clinical alkalosis are variable. The earliest symptoms may be simply a distaste for powders and food (especially milk

and cream). Lassitude, weakness, headache, nausea and vomiting may be early symptoms, or they may appear later. All variations from mild drowsiness to stupor and coma have been observed. Mental symptoms varying from slight changes in personality (such as irritability and lack of cooperation) to disorientation and irrationality have been noted. The more severe mental symptoms were seen especially in older patients with evidence of arteriosclerosis. Tetany and muscular twitchings, described by several authors, have been notably absent. Shock and Hastings [32] stated the belief that a marked decrease in partial carbon dioxide tension is the cause of tetany in disturbances of the acid-base balance. This would occur primarily in hyperventilation.

A striking lack of correlation has been observed between the severity of symptoms and the degree of chemical alkalosis. Data for 9 selected patients (table 3) illustrates this. In patients F. C. and M. V. characacteristic symptoms of alkalosis developed during treatment for ulcer. The values for the blood of F. C., however, were entirely normal, and those for the blood of M. V. only slightly elevated, the elevation being no greater than that usually observed for patients receiving a Sippy type of treatment. In contrast to these, patients *26* and *22* had no symptoms during the period when the acid-base balance shifted markedly to the alkaline side. The values for patient 18 are characteristic of those in the usual case in which severe symptoms accompanied the marked chemical alkalosis; however, it will be noted that the chemical alkalosis was less severe than that in patients *26* and *22*, who had no symptoms. In patient 24 (see also chart 4) the symptoms and chemical composition of the blood were not correlated from day to day. In patient 8 the symptoms may well have been related to the retention of nitrogenous products rather than to the alkalosis. These findings suggest that symptoms of alkalosis do not depend on a definite threshold of chemical alkalosis.

URINARY EXCRETION OF SOLIDS DURING TREATMENT FOR PEPTIC ULCER

In addition to their normal function, the kidneys are required to assume a considerable extra burden during the Sippy type of treatment. The excretion of large amounuts of bicarbonate has been demonstrated. It is likely that the excretion of the basic ions is proportionately even greater, for, of that part of the ingested alkali which is used to neutralize gastric acidity, the bicarbonate escapes as gaseous carbon dioxide by belching, thereby leaving the basic ions for the kidneys to excrete. As a measure of this extra work, the total solids excreted by the kidneys

32. Shock, N. W., and Hastings, A. B.: Studies of the Acid-Base Balance of the Blood: IV. Characterization and Interpretation of Displacement of the Acid-Base Balance, J. Biol. Chem. **112**:239 (Dec.) 1935.

was determined. Similar determinations were made on a group of nonulcerous patients, as controls.

The concentration of solids in the twenty-four hour specimen of urine was estimated by multiplying the last two figures of the specific gravity by 2.3 (Haeser's coefficient [33]). The total solids was calculated in grams by multiplying this product by the volume of the specimen (in

TABLE 3.—*Lack of Relation of Symptoms to Chemical Alkalosis*

Patient (Alkalosis Series)	Date	Symptoms	p_H	Carbon Dioxide Content, mM/L.	Serum Chlorides, mM/L.	Urea Nitrogen, Mg. per 100 Cc.	Comment
F. C. (not in alkalosis series)	May 11, 1935	Headache; fatigue; listlessness	7.40	28.1	..	....	Symptoms of alkalosis while receiving alkali therapy, but normal blood chemistry
M. V. (not in alkalosis series)	Sept. 17, 1934	Headache; nausea; vomiting; distaste for powder	7.53	33.1	..	....	Typical symptoms of alkalosis while receiving alkali therapy, but p_H and CO_2 only slightly elevated
26	Feb. 25, 1937	No symptoms	7.63	46.0	80	....	Marked chemical alkalosis without symptoms
22	Nov. 2, 1933 Nov. 4, 1933	No distress Still no distress	7.62	52.4	..	28.4	Same as for patient 26
18	Jan. 21, 1934	Semicoma; irrationality; disorientation	7.56	44.4	..	....	Severe symptoms with less chemical alkalosis than in patients 26 and 22
25	March 8,1937	Drowsiness	7.73	55.2	70	45.0	See chart 2
4	June 1, 1933	Drowsiness from which patient was easily aroused; irrationality	7.68	55.1	..	....	
24	June 16, 1935	No symptoms	7.68	40.0	..	....	Lack of correlation
	June 17, 1935	Distaste for powder and for milk and cream	7.60	40.5	..	21.6	between symptoms and degree of shift of acid-base balance
	June 18, 1935	Lassitude; severe headache; nausea and vomiting	7.60	35.3			from day to day (see charts 4 and 5)
8	June 17, 1932	Disorientation; irrationality	7.69	49.2	..	78.0	Symptoms and retention of nitrogen
	June 18, 1932	Coma; convulsions	7.59	46.0	..	90.0	progressing to fatal
	June 19, 1932	Patient died in coma	7.50	31.4	..	98.0	end, while acid-base balance improved

liters). The total solids excreted in the urine was then expressed in terms of grams per kilogram of body weight per twenty-four hours.

The total twenty-four hour urinary excretion of solids was determined twenty-five times for 3 patients undergoing treatment for ulcer. It was found to vary from 0.9 to 1.5 Gm. per kilogram of body weight, the average being 1.24 Gm. Determinations on 95 twenty-four hour

33. Seifert, O., and Mueller, F.: Manual of Physical and Clinical Diagnosis, ed. 2, translated by E. C. Andrus, Philadelphia, J. B. Lippincott Company, 1934, p. 186.

specimens from the control series of 6 persons [34] showed the total solids to vary from 0.3 to 1 Gm. per kilogram per twenty-four hours, the average being 0.63 Gm. Thus, the average urinary excretion of solids of patients undergoing treatment for ulcer was nearly twice as great as that of patients in the control group. These data are presented graphically in chart 6.

A CLINICAL STUDY OF TWENTY-EIGHT PATIENTS IN WHOM CLINICAL ALKALOSIS DEVELOPED DURING TREATMENT FOR PEPTIC ULCER

During a ten year period (1928 to 1937), moderate to severe clinical alkalosis developed in 28 patients undergoing treatment for ulcer at the

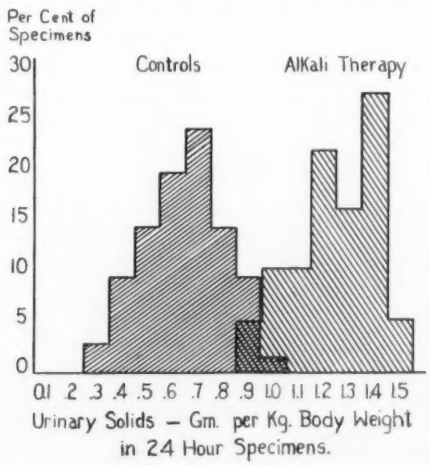

Chart 6.—The daily excretion of solids by the kidney during alkali therapy (25 specimens) as compared to that in a control group (95 specimens).

University of Chicago Clinics. The case histories of these patients were critically reviewed with the special purpose of evaluating any evidence for the existence of renal damage prior to the onset of alkalosis. The group consisted of 26 men and 2 women. The ages ranged from 35 to 75 years, the average being 52 years. Nine patients were 60 years of age or older. Five patients had gastric ulcers, and 24 had

34. The control group was made up of 2 patients with pulmonary tuberculosis on high caloric diets, 1 patient with tuberculous pleural effusion during the resorption stage, 1 patient with arthritis with fever, 1 patient with advanced Hodgkin's disease with fever and 1 normal man engaged in his usual occupation.

duodenal ulcers. (One had both gastric and duodenal ulcers.) Fourteen patients had moderate to severe stenosis.

Nineteen patients showed evidence of preexisting renal damage. The data for 3 additional patients were suggestive of renal damage but were not conclusive. Of the remaining 6 patients, the data for 4 were

TABLE 4.—*Evidence of Renal Damage Found in the Alkalosis Series*

Case No.	High Blood Pressure	Low Urea Index	Anemia	Arteriosclerosis	Prostatism	Other Findings	Autopsy Data*	Summary
1	+	..	..	..	..	Bilateral renal calculi	.....	++
3	+	+	+	+	..	.....	.....	++++
4	..	..	+	+	..	.....	.....	++
5	..	+	+	..	..	.....	.....	++
6	+	..	..	..	+	.....	.....	++
7	+	..	..	..	+	.....	.....	++
8	+	..	..	..	..	Nephrectomy	Old nephrectomy; remaining kidney showing subacute interstitial nephritis	+++
9	+	..	..	+	+	.....	Pyelonephritis; essential hypertension	++++
11	..	..	..	+	..	.....	.....	+
15	..	+	..	..	..	.....	.....	+
17	..	+	..	..	..	Renal colic	.....	++
18	+	+	..	+	..	Calcified blood vessels; albumin and erythrocytes in urine; urea nitrogen in blood, 41 mg. per cc.	.....	++++
19	+	..	..	..	..	.....	.....	+
20	..	+	+	..	..	.....	.....	++
21	..	+	+	..	..	.....	Arteriosclerotic kidneys	+++
22	+	..	..	..	..	.....	.....	+
23	..	+	+	..	..	.....	.....	++
24	+	..	+	+	+	.....	Arteriosclerosis	+++++
25	+	+	..	..	..	.....	.....	++
26	+	..	..	+	..	.....	.....	++
27	+	..	+	+	..	.....	Atrophy of kidneys; arteriolar arteriosclerosis	++++
28	+	..	+	..	+	.....	.....	+++
Total	14	9	9	8	5	4	5	

* In addition to the 5 autopsies, there were 5 deaths without autopsy within one year of the attack of alkalosis. Of the 10 deaths, 3 were attributed to the alkalosis.

considered inadequate to form conclusions, and that for the other 2 suggested normal kidneys but lacked the completeness desirable to prove that the kidneys were unimpaired. Unfortunately, careful studies of the renal function were not made routinely before starting therapy. The evidence for preexisting renal impairment in the 19 patients classified as having suffered previous damage to the kidneys and in the additional 3 suspected is summarized in table 4. The data are listed under seven

criteria. In the majority of cases two to five of the criteria were present. Anemia was present in 9 cases, but in all of them other criteria were present also. That anemia in itself can be a cause of low renal function has long been known. In 1915 Mosenthal [35] observed that in severe anemia, whether of primary or secondary type, tests of renal function give results similar in all respects to those described in cases of contracted kidney in the advanced stages. The cure of the anemia was noted to be followed by great improvement in the renal function. Christian,[36] Stieglitz,[37] Fishberg [38] and others have noted similar phenomena, especially in pernicious anemia. Fishberg stated the belief that the low renal function in anemia is due to malnutrition of the kidney cells and more particularly to a reduced supply of oxygen.

COMMENT

Various phases of the present investigation emphasize the great importance of renal function in the causation of alkalosis. It has been demonstrated that a greatly increased burden is placed on the kidneys during alkali therapy. Studies of fluid balance show that during treatment for ulcer, fluid intake and urinary output are increased. Some of the patients commented on the frequency of urination, especially the nocturia, which they experienced. Because of the likelihood that the kidneys might require a volume of water greater than normal to perform their extra work, three day periods of limitation of fluid were instituted to note whether renal compensation would fail. In the 2 patients so studied, the kidneys were able to continue their function in spite of this handicap, but the body went into a negative fluid balance during these periods.

Estimation of the total urinary excretion of solids suggest that the kidneys' work is nearly doubled during alkali therapy. It is not surprising, then, that diseased kidneys may fail in this task. Kidneys with a low functional reserve may be able to perform the work required by normal life without showing evidence of strain or of disease, but when the added burden of alkali therapy is imposed on them their functioning may prove inadequate, and alkalosis may ensue. The situation is analogous to that of a heart with a low functional reserve which carries the patient through the ordinary activities of life without effort or

35. Mosenthal, H. O.: Renal Function as Measured by the Elimination of Fluids, Salt, and Nitrogen, and the Specific Gravity of the Urine, Arch. Int. Med. **16**:733 (Nov.) 1915.

36. Christian, H. A.: Renal Function in Pernicious Anemia as Determined by Dietary Renal Tests, Arch. Int. Med. **18**:429 (Oct.) 1916.

37. Stieglitz, E. J.: Disturbances of Renal Function in Pernicious Anemia, Arch. Int. Med. **33**:58 (Jan.) 1924.

38. Fishberg, A. M.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934.

evidence of disease but which decompensates when an additional burden, such as pregnancy or severe infection, is placed on it.

Analysis of the clinical data for 28 patients with alkalosis further confirms the opinion that impaired renal function is of the highest etiologic significance in alkalosis. In the majority of the patients there was a correlation between preexisting renal disease and the development of alkalosis. Most of the patients were in the older age groups, in which a high incidence of arteriosclerotic renal disease may be expected. It is unfortunate that comprehensive studies of renal function were not made routinely before the onset of alkali therapy. If such studies were made, they probably would show that alkalosis develops only in patients with either definite renal disease or a low renal reserve. Exceptions may occur in cases of pyloric obstruction in which there is an excessive loss of gastric contents.

In most cases low renal reserve will remain undetected unless especially sought. Evidence of the condition may not appear on the usual routine clinical study, nor will a history of renal disease necessarily be present. Special studies of renal function are necessary. Which one of the many available tests of renal functions is best suited to measure the function of the kidneys with special reference to their ability to carry the burden of alkali therapy? A direct answer to this question is not available. Wilkinson and Jordan [39] have successfully used the sulfate clearance test for this purpose. Alving and Van Slyke [40] have shown that, in general, the urea clearance test measures the function of excreting nitrogen, while concentration tests measure the function of excreting mineral salts. Freyberg [41] compared the efficiency of most of the popular tests of renal function. He concluded that only during the concentration tests are conditions such that the renal function is measured while the kidneys are under functional strain and that therefore it is the only test designed to measure maximal function. The concentration test registers impairment of function when other tests do not, and it is therefore the most sensitive measure of renal efficiency. The urea clearance test may give a better conception of the degree of renal impairment, but it is considerably less sensitive in detecting early impairment of function.

It is not enough to exercise great care in administering alkalis to patients with evidence of renal disease. Among patients with ulcers those with low renal reserve must also be discovered and treated cautiously if alkalosis is to be avoided. Therefore, before starting intensive alkali therapy for any patient, a study of the functioning of

39. Wilkinson, S. A., and Jordan, S. M.: Significance of Alkalosis in Treatment of Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **1**:509 (Sept.) 1934.

40. Alving, A. S., and Van Slyke, D. D.: The Significance of Concentration and Dilution Tests in Bright's Disease, J. Clin. Investigation **13**:969 (Nov.) 1934.

41. Freyberg, R. H.: The Choice and Interpretation of Tests of Renal Efficiency, J. A. M. A. **105**:1575 (Nov. 16) 1935.

his kidneys while under functional strain is indicated. If alkali therapy is to be prolonged, interval studies of renal function are worth the effort. Special care is also indicated in alkali therapy following hemorrhage.

Some experiments suggest that the prolonged administration of alkali may produce damage to the kidneys. Addis and his associates [42] found that prolonged administration of alkalis to rats produced gross or microscopic hematuria in all cases, but at autopsy no lesions were noted in the kidneys. Nuzum and his associates [43] showed that long-continued alkalinization caused moderate hypertension and renal damage in rabbits. Stieglitz [44] stated the belief that during alkali therapy the excretion of alkaline urine is irritating and causes renal damage. On the other hand, Kellert [45] gave rabbits intravenous injections of sodium bicarbonate and failed to observe any injurious effects on the kidneys or any aggravation of preexisting experimental nephritis. Steele [46] reported a case suggesting that the prolonged administration of alkalis may produce renal damage and impaired function. The renal function, however, was not studied before the alkali therapy was started.

In 1 patient in the present series signs of essential hypertension with decreased renal function developed while alkali therapy was being administered.

Patient 22, a 31 year old man, was first given alkali treatment for an uncomplicated duodenal ulcer in April 1931. At that time his blood pressure was 128 systolic and 80 diastolic and 130 systolic and 86 diastolic on two occasions. The standard urea clearance was 60 before the administration of alkalis was begun and 42 after ten days of treatment. Clinical alkalosis was not present, and chemical alkalosis was not unusual. In October 1933, after having taken alkali powders most of the intervening time, he was readmitted to the hospital after a massive hemorrhage. At that time his blood pressure was 185 systolic and 110 diastolic. After five days of alkali therapy in the hospital, alkalosis developed. His blood pressure then was 200 systolic and 115 diastolic, and his standard urea clearance had dropped to 25. He recovered from the hemorrhage, the anemia and the alkalosis uneventfully. He has been followed in the clinic until the time of writing and has continued to show hypertension and low urea clearance. He has taken little alkali since 1933.

Clinical experience suggests that most patients tolerate alkali powders over long periods and escape without renal damage. It cannot

42. Addis, T.; MacKay, E. M., and MacKay, L. L.: The Effect on the Kidney of the Long-Continued Administration of Diets Containing an Excess of Certain Food Elements, J. Biol. Chem. **71**:157 (Dec.) 1926.

43. Nuzum, F. R.; Seegal, B.; Garland, R., and Osborne, M.: Arteriosclerosis and Increased Blood Pressure, Arch. Int. Med. **37**:733 (June) 1926.

44. Stieglitz, E. J.: Alkalis and Renal Injury, Arch. Int. Med. **41**:10 (Jan.) 1928.

45. Kellert, E.: The Action of Intravenous Injections of Sodium Bicarbonate upon the Kidneys, Am. J. M. Sc. **167**:114 (Jan.) 1924.

46. Steele, J. M.: Renal Insufficiency Developing During Prolonged Use of Alkalis, J. A. M. A. **106**:2049 (June 13) 1936.

be denied, however, that an occasional patient may sustain injury to his kidneys. Almost certainly, preexisting renal disease may be aggravated.

What are the factors which determine the symptoms of alkalosis? The lack of correlation between clinical alkalosis and chemical alkalosis, even in the same patient, suggests that symptoms do not depend on a definite threshold of chemical alkalosis. It is possible that symptoms may be related to a cumulative effect of a prolonged displacement of the acid-base balance. Wildman [47] suggested that they are related to a decrease of chlorides in the plasma. Because of the usual reciprocal relationship between serum bicarbonate and serum chlorides (chart 2), it is not possible to evaluate directly the effect of deviation of chlorides on the symptoms. Similarly, it is difficult to evaluate the effect of depletion of chlorides in cases in which deviation of acid-base balance is not present, for in such cases changes in water balance and in total base occur. Peters and Van Slyke [48] stated the belief that toxic symptoms arising in connection with depletion of chlorides are probably due to these factors rather than to the depletion of chlorides. It should be noted that in cases of heat cramp and heat exhaustion a marked diminution of serum chlorides occurs with minimal changes in the other constituents of the blood (Shoudy and Baetjer [49]) and that in these conditions the symptoms are different from those seen in alkalosis.

CONCLUSIONS

1. Tolerance to alkalis usually develops during the Sippy type of treatment for peptic ulcer.

2. In all patients receiving alkali therapy some degree of chemical alkalosis develops, but clinical alkalosis develops in few.

3. Symptoms of alkalosis are not correlated with the degree of chemical alkalosis present.

4. During alkali therapy the work of the kidney is greatly increased. The urinary excretion of solids was found to be nearly doubled.

5. In the patients in whom clinical alkalosis developed during alkali therapy for peptic ulcer a high incidence of preexisting renal damage was found.

Dr. A. B. Hastings and Dr. Lillian Eichelberger advised concerning the biochemical problems. Dr. George F. Dick and Dr. Walter L. Palmer permitted the use of clinical material.

47. Wildman, H. A.: Chloride Metabolism and Alkalosis in Alkali Treatment of Peptic Ulcer, Arch. Int. Med. **43**:614 (May) 1929.

48. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 1.

49. Shoudy, L. A., and Baetjer, A. M.: Heat and Muscular Work, Surg., Gynec. & Obst. **62**:475 (Feb.) 1936.

STAPHYLOCOCCIC SEPTICEMIA

A REVIEW OF THIRTY-FIVE CASES, WITH SIX RECOVERIES, TWENTY-NINE DEATHS AND SIXTEEN AUTOPSIES

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Contrary to common opinion, the staphylococcus is the deadliest organism of general sepsis. This bacterium, universal in distribution and of extremely low virulence, is generally considered to be a secondary invader, leading a saprophytic existence on the skin and mucous membranes of the body and producing small pimples, furuncules and abscesses. It is not fully appreciated that at the same time it is also capable of producing the most dangerous of all septicemias. From the most insignificant site of infection, even a microscopic abrasion of the skin, the staphylococcus may invade and infect the blood stream, with a resulting fatal outcome due to the formation of septic embolic foci or abscesses in all the organs of the body, and with the occurrence particularly of septic bronchopneumonia, metastatic abscesses and degeneration of the kidneys, liver and heart.

The incidence of staphylococcic septicemia is also greater than is commonly thought. About two thirds of all cases of septicemia are due to the streptococcus, principally Streptococcus haemolyticus; Stevens [1] has made an estimate of 60 per cent and Brookhart [2] an estimate of 80 to 90 per cent. Rosenow Jr. and Brown [3] have given the ratio of streptococcic septicemia to staphylococcic septicemia as 2:1. Neuhof and his co-workers [4] have estimated the incidence of streptococcic septicemia in comparison with that of staphylococcic septicemia as 3:2. In the present series, excluding the cases of septicemia due to Streptococcus viridans from the total number of cases of streptococcic septicemia, the

1. Stevens, F. A., in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1929, vol. 1, p. 1298.

2. Brookhart, E. B.: Staphylococcic Septicemia, M. Sentinel **38**:9-12 (Jan.) 1930.

3. Rosenow, E. C., Jr., and Brown, A. E.: Septicemia: A Review of Cases, 1934-1936 Inclusive, Proc. Staff Meet., Mayo Clin. **13**:89-93 (Feb. 9) 1938.

4. Neuhof, H.; Aufses, A. H., and Hirshfeld, S.: Pyogenic Sepsis: Survey of One Hundred and Fifty Cases, Surg., Gynec. & Obst. **58**:886-896 (May) 1934.

incidence of streptococcic septicemia in comparison with that of staphylococcic septicemia was 2.3:1 (80 cases of the former and 35 of the latter).

This study was prompted by the unusual occurrence of recovery in 3 cases of staphylococcic septicemia during the spring and summer of 1937, by the fact that only 3 other patients with staphylococcic septicemia have recovered in the past eight years in the Mount Sinai Hospital, and, also, as stated in other reports, by a desire to encourage others in the care of patients with this desperate disease; for some of these patients do recover, sometimes when it is least expected.

While it was thought at first that the records of this hospital would yield more than 35 cases of staphylococcic septicemia over the period studied, the rigid criteria accepted for the diagnosis of staphylococcic septicemia were more responsible for limiting the total number than any other factor. There were many cases of staphylococcic infection with severe toxemia, many cases of transient staphylococcic bacteremia and many cases in which blood cultures of the staphylococcus were obtained agonally from a patient dying of other causes wherein staphylococci secondarily invaded the blood stream owing to the patient's debilitated state. Such cases were discarded and not used in this report. It is well known that harmless transient staphylococcic bacteremia does occur without septicemia, and cases have been reported as occurring after minor surgical procedures, such as extraction of a tooth or tonsillectomy (Fischer and Gottdenker [5]).

In the selection of cases for this study, Kolmer's [6] definition of staphylococcic septicemia was chosen as the criterion: "an infection of the blood by staphylococci, their pathogenic presence and products in the blood, associated with infection of fixed tissues resulting in severe constitutional disturbances with the signs of sepsis." The blood may be invaded by pathogenic organisms without the appearance of any signs of infection, and for that state the term bacteremia is used instead of septicemia.

MORTALITY

The mortality for staphylococcic septicemia is very high. It is a deadly disease, and in most cases when the diagnosis is made it is already beyond control. Some authors place the mortality as high as 90 per cent. Reimann,[7] reviewing the literature on infections, made the state-

5. Fischer, J., and Gottdenker, F.: Ueber transitorische Bakterieneinschwemmung in die Blutbahn nach Tonsillektomie, Wien. klin. Wchnschr. **49**:177 (Feb. 7) 1936.

6. Kolmer, J. A.: Septicemia, Ann. Int. Med. **8**:612-631 (Nov.) 1934.

7. Reimann, H. A.: Infectious Diseases: Review of the Current Literature, Arch. Int. Med. **58**:329-370 (Aug.) 1936.

ment that the average mortality for the disease is 79 per cent. Scott,[8] in a series of 79 cases, reported a mortality of 79 per cent. Bean [9] reported 9 cases, with 1 recovery, a mortality of 89 per cent. Neuhof [4] divided his cases as follows: those due to osteomyelitis (27 cases), with a 56 per cent mortality, and those due to carbuncle (17 cases), with an 82 per cent mortality. MacNeal and Frisbee [10] reported the use of bacteriophage in 100 cases, with a mortality of 75 per cent. These authors stated that prior to 1929 any case of staphylococcic septicemia in which two consecutive blood cultures gave positive results was invariably fatal. Rosenow Jr. and Brown [3] reported 29 cases, with a mortality of 66 per cent. Lowenstein [11] reported the occurrence of 18 cases in nine years at the Jewish Hospital in St. Louis, with only 3 recoveries.

In the present 35 cases (for 1929 to 1937, inclusive) there were 29 fatalities and 6 recoveries (a mortality of 83 per cent). Certain factors definitely influenced the mortality rate, as for instance the presence of associated diseases. There were 9 such cases: 6 of diabetes mellitus, 2 of hypertensive cardiovascular disease and 1 of rheumatic carditis. All of these patients died. The age factor was also of importance; recovery occurred in none of the patients in the first decade of life. The sthenic age group fared best, as shown in other reports. Of the 6 who recovered, 5 were between the ages of 13 and 33 years; the sixth patient was 53 years old. Although in the majority of cases (27) the septicemia originated from infections of the skin (e. g., carbuncles, abscesses and furuncles) or of bone (acute osteomyelitis), only these two sites were involved in the cases in which recovery occurred; all other sites of origin were noted in fatal cases, e. g., the prostate, sinuses and heart. Twelve of our patients were females, and all died. This was merely a coincidence in this series, the disease being no more fatal in females, although the incidence is higher in males. In reviewing the series for the cause of this unusual occurrence, it was found that of the 12 females, 6 were very young, most of them being in the first decade of life, wherein the total mortality was highest; only 1 was in the favorable sthenic age group, wherein the most recoveries occurred. Of the 12 females, 4 had diabetes mellitus. All these factors added to the

8. Scott, W. J. M.: The Principles of the Treatment of Septicemia, J. A. M. A. **105**:1246-1249 (Oct. 19) 1935.

9. Bean, H. C.: Clinical Study of One Hundred and Nine Cases of Septicemia, M. Sentinel **37**:679-686 (Dec.) 1929.

10. MacNeal, W. J., and Frisbee, F. C.: One Hundred Patients with Staphylococcus Septiçemia Receiving Bacteriophage Service, Am. J. M. Sc. **191**:179-195 (Feb.) 1936.

11. Lowenstein, P. S.: Staphylococcus Septicemia, Am. J. M. Sc. **181**:196-203 (Feb.) 1931.

gravity of the disease and denoted in this series that the females were in the group showing a more unfavorable prognosis—hence the high mortality.

Certain complications during the course of the septicemia influenced the mortality, for example, the occurrence of staphylococcic meningitis. There were 7 such cases; all were fatal.

SEX AND AGE

The ratio of males to females was nearly 2 to 1 (23 males and 12 females). This is in accord with the ratio given for other series reported in the literature.

The age groups were as follows:

Age	Fatal Cases	No. of Recoveries
1 to 9	5	0
10 to 19	7	3
20 to 29	5	1
30 to 39	3	1
40 to 49	4	0
50 to 59	3	1
60 to 69	2	0
	29	6

The disease occurs at all ages, from infancy to senility. The youngest patient was 1 year old and the oldest 69. The incidence was about the same throughout the age groups, possibly slightly higher in early age groups, owing to the increased incidence of osteomyelitis in childhood; but this was nearly offset by the increased incidence of infections of the skin in later life. Twenty-one patients were under 30 and 14 were over 30. In none of the females was the site of origin in the female generative tract, whereas in the males the disease not infrequently originated in this tract. Osteomyelitis was more prevalent in the younger age groups, 10 of the 13 patients being less than 20 years old; whereas infections of the skin were more common after the age of 20, 11 of the 14 patients being in that age group.

SITES OF INFECTION

Skin.—There were 14 cases in which the portal of entry was the skin (5 females and 9 males, 3 being under 20 years of age and 11 over 20). Six patients had carbuncles, and 1 recovered; 4 had abrasions of the skin, and 2 recovered; 4 had abscesses or furuncles and 1 recovered. The total mortality for this group was 71 per cent.

In the 10 fatal cases the average length of life of the patients in this group after the blood culture was established as positive was five and one-half days.

Osteomyelitis.—There were 13 cases of osteomyelitis (7 females and 6 males, 10 being under 20 years of age and 3 over 20). There were 2 recoveries, the patients being 18 and 13 years old, respectively. In the 11 fatal cases the average length of life after blood culture gave positive results was five days. In 5 cases the infection originated in the tibia, with no recoveries; in 2 in the pubic bone, with 1 recovery; in 2 in the humerus, with 1 recovery; in 1 case in the os calcis and in 1 case in the mastoid bone, both being fatal. The total mortality for this group was 85 per cent.

Prostatic Abscess.—There were 3 cases of prostatic abscess, and all were fatal. The ages of the patients were 39, 30 and 54 years, respectively. The average length of life after blood culture gave positive results was seven days.

Infection of the Nasal Sinuses.—There were 2 patients with infection of the nasal sinuses, both of them boys, aged 12 and 17, respectively; 1 died three days and the other six days after surgical intervention. Meningitis was the cause of death in both cases.

Miscellaneous Infections.—There were 3 other cases of infection, and all were fatal: One originated in a dental infection in a 27 year old man with rheumatic carditis, 1 originated in pulmonary abscess in a 19 year old boy and 1 originated in staphylococcic endocarditis in a 37 year old man.

DURATION OF THE DISEASE

Staphylococcic septicemia is a desperate disease and as a rule is quickly and violently fatal. Often a patient succumbs before therapeutic procedures have had an opportunity to act. If life can be maintained past the first week or ten days, the prognosis is greatly enhanced. Of the 29 patients who died, 27 were in the hospital for a total of three hundred and forty days, or an average of twelve and one-half days. This group lived a total of a hundred and fifty-five days after positive results of blood culture were established, or an average of five and seven-tenths days, the shortest duration of life being one day (osteomyelitis of the tibia in a girl aged 1 year) and the longest being fifteen days (osteomyelitis of the mastoid bone with terminal staphylococcic meningitis). The 2 other patients who died (considered separately because the behavior of the disease was unlike that of true staphylococcic septicemia) lived one hundred and eighty-five days in the hospital, or an average of ninety-two and one-half days. One had chronic bacterial endocarditis (Staphylococcus albus haemolyticus), and the clinical course was more like that of endocarditis lenta than of staphylococcic septicemia. The other had

rheumatic carditis with a dental infection which resulted in staphylococcic septicemia, death resulting from embolic septic bronchopneumonia due to staphylococci.

For the 6 patients who recovered, the total period of hospitalization was four hundred and fifty-four days, or an average of seventy-six days. If one contrasts this average of seventy-six days with that of twelve and one-half days of life in the fatal cases, one can well appreciate the old clinical dictum that the longer a patient with staphylococcic septicemia lives, the more favorable the ultimate outcome. Positive results of blood culture were obtained for an average of fourteen days for this group of 6 patients, the shortest period being five days (a 54 year old man with an abscess of the leg and septic thrombophlebitis) and the longest continuous period being thirty-two days (a 33 year old man with a carbuncle on the back; case 1).

LABORATORY DATA

Staphylococcus aureus haemolyticus was responsible in 33 of the 35 cases and Staph. albus haemolyticus in 2 cases. The infections due to the latter organism were both fatal: 1 case of staphylococcic endocarditis and 1 of violently acute osteomyelitis of the os calcis, the patient living only six days. The 6 recoveries occurred among patients with infections due to Staph. haemolytic aureus.

The organism was recovered from the portal of entry in 31 cases before or during operation and was similar to the organism cultured from the blood. In the 4 other cases the data were as follows: Death occurred in one day in 1 case, and the organism was recovered post mortem from the portal of entry; in 1 case of prostatic abscess the organism was recovered post mortem; in the fatal case of staphylococcic endocarditis a smear could not me made ante mortem, and postmortem examination was not permitted; in 1 case of acute osteomyelitis, recovery was obtained under conservative management without operation, so that no smear could be made.

Peripheral Blood Picture.—The picture of the peripheral blood was difficult to evaluate, as many of the patients did not live long enough for anemia to develop. For those who did survive for any length of time, repeated blood transfusions influenced the picture favorably. Therefore, anemia was not the rule. Eighteen patients showed a hemoglobin percentage between 80 and 100 per cent; 9, between 70 and 80 per cent; 7, between 60 and 70 per cent, and 1 between 50 and 60 per cent. The erythrocyte levels corresponded. The red blood cell count was between 4,000,000 and 5,000,000 in 20 cases, between 3,000,000 and 4,000,000 in 14 cases and below 3,000,000 in 1 case. In the patients with severe infection who lived longer than one week, anemia occurred

and was a problem, in spite of repeated transfusions. Anemia may be expected because of two factors: the long-sustained infection, with its toxic effect on the erythroblastic function, and the hemolytic character of the organism.

The leukocyte level was of more clinical value. Leukocytosis was the rule. Seven patients showed total white blood cell counts above 30,000, 2 showed total counts below 10,000, 26 showed counts between 10,000 and 30,000 and the majority showed counts around 20,000. The 6 who recovered showed counts between 10,000 and 30,000. Too high or too low a total leukocyte count was unfavorable in this series. The polymorphonuclear neutrophil count was increased in 34 of the 35 cases as follows: In 29 it was between 80 and 100 per cent, in 5 it was between 70 and 80 per cent and in only 1 was it less than 70 per cent.

The Schilling index was obtained in only 8 cases of the series, in all of which there was a marked shift to the left, with more than 30 young forms. The degenerative index [12] was obtained in only 7 cases and was between 90 and 100 per cent. All of these cases were fatal.

Urine.—The urine showed the effects of toxic parenchymatous changes in the kidneys in 25 cases by the presence of albumin, red blood cells, casts or pus. In 16 cases the urine contained acetone, denoting associated acidosis due to the severity of the infection.

Blood Cultures.—Total colony counts were not routinely reported. In every case blood culture was positive. Each blood culture was rechecked and found to be positive on more than one occasion, with the exception of 4 cases in which death occurred in forty-eight hours or sooner. In 2 of the 4 cases a postmortem examination was made, and the organism cultured from the heart blood corresponded to the one cultured from the blood during life.

CLINICAL COMPLICATIONS

The complications were found by physical examination, roentgenography or laboratory study. Thirty of the 35 patients presented such complications, and 5 escaped without the detection of extension of the infection to other organs. In the majority of cases the complications consisted of the production or the development of a secondary focus of suppuration in a fixed organ or tissue. Extension of the infection or complication is the rule in this disease. Failure to demonstrate such secondary extension of the disease during life may be due to the fact that it occurs in a silent organ, defeating measures of detection and also to the fact that the grave state of the patient often prevents thorough search for foci.

12. Mendell, T. H.; Meranze, D. R., and Meranze, T.: Comparative Study of Cytoplasmic and Nuclear Changes in Neutrophils in Severe Infectious States, Am. J. M. Sc. **192**:316-327 (Sept.) 1936.

There were no set rules as to the number or types of complications that developed, no particular sites of complications were predilected and there was no relation between the number of complications and the death rate. In general, the fewer the number of complications, the lower the mortality; yet this did not hold absolutely, as shown in cases 1 and 2, in which recovery occurred in spite of numerous complications that were almost impossible to overcome. The opposite also occurred; several patients succumbed to violent toxemia before complications could develop. The lungs and kidneys were most frequently involved in this series. This is borne out by experimental data,[13] which have shown that staphylococci can be injected into the blood stream of animals and within a few hours recovered from the pulmonary tissues.

Twenty-four of our patients showed pulmonary complications in the nature of septic bronchopneumonia, pulmonary abscesses, pleuritis, atelectasis or empyema. In these 24 cases the complication was secondary to osteomyelitis in 11 cases, to infections of the skin in 10 cases, to prostatic abscess in 1 case and to infection of the nasal sinuses in 2 cases. The kidneys were involved in 25 cases, as shown by abnormal urinary findings, denoting toxic parenchymatous changes; renal abscesses or carbuncles were single or multiple in 9 cases, the diagnosis being established roentgenographically, by the presence of pyuria or staphylococcuria or at operation. The renal complications were secondary to osteomyelitis in 13 instances, cutaneous lesions in 9, prostatic abscess in 1, sinus infection in 1 and pulmonary abscess in 1. The skin was secondarily involved by multiple metastatic abscesses in 10 cases, the original focus being osteomyelitis in 4, carbuncles in 3, a prostatic abscess in 2 and sinus infection in 1. The meninges and brain were involved in 7 cases, as proved by the clinical signs of meningitis and the recovery of staphylococci and pus from the spinal fluid. All were fatal. One case was due to osteomyelitis, 2 to sinus infection, 1 to carbuncle, 1 to a furuncle of the skin, 1 to a prostatic abscess and 1 to a pulmonary abscess. Toxic myocarditis occurred in 4 cases, as shown by toxic changes in the electrocardiogram. It is probable that this complication exists more frequently, because in this series electrocardiographic study was made in only 4 cases and in each of these showed changes. Secondary metastatic suppurative arthritis occurred in 4 cases, 2 being of osteomyelitic and 2 of cutaneous origin. Secondary osteomyelitis occurred in a case of primary osteomyelitis. Parenchymatous hepatitis occurred in 2 cases of cutaneous origin. Suppurative subacromial bursitis occurred as a sequela in a patient who recovered (four months after the blood culture had been sterile; case 1).

13. Wysokowitch, cited by Willetts, E. W.: Blood Stream Infections, Pennsylvania M. J. **36**:312-317 (Feb.) 1933.

Four patients had no demonstrable complications. One was a case of osteomyelitis of the pubic bone treated by incision and drainage, with fatal outcome and no postmortem examination. In 3 cases recovery resulted without clinical complications: a case of cellulitis of the forearm, with positive results of blood culture obtained for eight days; a case of furuncle and thrombophlebitis of the leg, with positive results of blood culture obtained for five days, and a case of osteomyelitis of the pubic bone, with positive results of blood culture obtained for nine days. In the 2 last mentioned cases there were only temporary toxic urinary changes.

Definite conclusions and calculations cannot be made from these figures, because they include only demonstrable complications, without any actual data regarding the true number of complications. Nevertheless, these figures are of interest in a comparative sense. The clinical complications numbered seventy-six in 31 of the cases, making an average of two and one-half complications per case. This figure may be compared with the following postmortem data regarding complications to determine how many conditions escape clinical detection.

POSTMORTEM DATA

In 16 of the 29 fatal cases autopsy was performed: 7 cases of infections of the skin (four carbuncles, two abscesses and one abrasion), 6 cases of osteomyelitis, 1 case of prostatic abscess, 1 case of dental infection and 1 case of sinus infection. In all these cases the effects of the severe infection circulating in the blood stream were evident, few organs escaping pyemic invasion or toxic degenerative changes due to sepsis. In the cases in which twelve hours before death few complications or no extension of infection was evidenced, marked multiple suppurative foci were present in the viscera. There was little relation between the source of the infection and the number of organs involved. The only constant factor was the organism.

The heart showed twenty-six different lesions, in the nature of cloudy swelling, muscle edema, septic vegetations on the valves, multiple myocardial abscesses, septic infarcts, suppurative pericarditis and hemopericardium. The majority of the cardiac complications occurred in the cases of osteomyelitic involvement.

The lungs and pulmonary structures demonstrated fifty-nine different lesions, in the nature of staphylococcic septic bronchopneumonia, bacterial septic infarcts and emboli, multiple pulmonary abscesses, fibrinous pleuritis, suppurative pleuritis, purulent bronchitis, edema, atelectasis and hemorrhage. The pulmonary complications occurred in all cases, regardless of the site of origin of the infection.

The kidneys yielded twenty-five complicating lesions, in the form of multiple abscesses (particularly cortical), bacterial emboli and septic infarcts, perirenal abscesses, purulent pyelitis, cloudy swellings and hemorrhage. These also occurred in all cases.

In each of the 16 cases in which autopsy was performed, one or more lesions were present in the lungs, heart and kidneys. These organs were the site of 60 per cent of the complications.

The spleen was affected 17 times by acute splenitis or by septic infarcts and in 8 cases by abscesses. The liver was involved in 12 cases, the lesions taking the form of cloudy swelling or fatty degeneration; abscess formation was noted in 5 cases and was usually of cutaneous origin. The adrenal glands were affected by degenerative and suppurative complications in 8 cases, the pancreas in 9 cases, the gastrointestinal tract in 5 cases, the skin and dermal structures by secondary abscesses in 9 cases and bone by osteomyelitis (in 6 cases primary and in 1 case metastatic) in 7 cases. The diaphragm showed an extensive abscess in 1 case, the lymph glands showed suppurative changes in 1 case, the urinary bladder was abscessed in 1 case of prostatic abscess and in 1 case the joints were involved by suppuration. The brain was the seat of multiple abscesses in 1 case, in which meningitis complicated the course. This was the only case in which postmortem study of the brain was granted, and it is possible that this complication would have been found more frequently had the opportunity for study been given. Aside from the hepatic complications, which occurred principally in the cases of infection of cutaneous origin, and the osseous complications, which ocurred only in the cases of osteomyelitis, the site of origin was of no influence with respect to the organs involved.

From these figures it will be seen that, on an average, twelve complicating lesions per case were present post mortem. It must be remembered that many of these complications existed during life in asymptomatic form or the sepsis so overwhelmed the patient that the symptoms were masked, thus defeating the diagnostic measures. However, the important point to be gathered from this postmortem study is that complications in staphylococcic septicemia are numerous, they involve most of the organs and they occur early. Failure to detect their presence clinically is in no measure a guarantee that they do not exist.

TREATMENT

It is difficult to evaluate any one therapeutic procedure in this disease. The gloomy outcome and the high mortality force the attending physician to utilize every possible aid which offers even the slightest hope of combating the extending infection. In the absence of specific treatment, the physician finds himself employing so many measures and remedies

that if cure does result, it is impossible to ascribe it to any one form of treatment. Then, too, the occasional occurrence of spontaneous cure adds doubt to the reputed success of certain remedies used in this disease. In many cases one form of remedy or another has been reported as successful which in the hands of other investigators has proved of no value. Yet, in spite of the meager knowledge of staphylococcic septicemia or of an effective treatment for it today, three cardinal principles for successful management stand out: (1) immediate and thorough eradication of the source of infection that is feeding the blood stream, (2) sterilization of the blood stream and (3) constant watch for the formation of metastatic foci, with prompt surgical eradication whenever possible.

Eradication of the Source of Infection.—This means quick and adequate surgical treatment—incision and drainage, excision or amputation if necessary. This cannot be overemphasized, as it is the most important single factor in recovery of the patient. The fact that the mortality for the disease is high in spite of adequate surgical treatment in many cases, does not subtract from the value of this all-important measure. No treatment can be successful without complete removal of the focus which is feeding and reinfecting the blood stream. Surgical treatment was employed in 31 of these 35 cases. The 4 cases in which it was not employed were as follows: the case of endocarditis, the case of osteomyelitis in which the patient lived only twenty-four hours, the case of thrombophlebitis and the case of osteomyelitis of the pubic bone in which recovery followed immobilization without incision. The 3 cases which will be cited in detail illustrate how futile treatment would have been without effective surgical eradication of the source.

Sterilization of the Blood Stream.—Today, unfortunately, there is not yet available a satisfactory disinfectant of the blood stream in staphylococcic septicemia. Until the time when there is at one's disposal as effective a remedy for staphylococcic infections as sulfanilamide has proved to be for streptococcic infections, one must rely on blood transfusions for sterilization of the blood. Repeated transfusions, preferably immunotransfusions, are of undisputed value. Transfused blood combats infection, counteracts anemia and supports the patient; the serum undoubtedly contains immunizing or neutralizing bodies effective against the staphylococcus. In 32 of the 35 cases repeated transfusions of whole blood were given, and the impression was gained that immunotransfusions were slightly superior to transfusions of citrated or of untreated blood. Of the 3 patients who were not given transfusions, 1 improved so promptly after incision into the infected area that transfusion was not necessary; 1 died in one day, before a donor could be found, and the third one had osteomyelitis of the pubic bone, with recovery by the closed method of treatment.

Chemotherapy: Chemicals were employed liberally; only a few patients of the entire series did not receive some disinfectant. It is of great doubt whether any chemotherapeutic agent in use today can be sufficiently concentrated in the blood stream during life to prove of absolute value against the staphylococcus. Many reported recoveries have been ascribed to various chemotherapeutic agents, but on careful review of these cases so many other factors are found to have entered into the treatment that the effectiveness of the germicide in itself cannot be gaged. In this series gentian violet was used in 16 cases, Pregl's iodine solution in 8, neoarsphenamine in 3, mercurochrome in 2, metaphen in 1, acriflavine in 1 and sulfanilamide in 3. Sulfanilamide not only did no good in these cases but in 1 case caused hepatitis with jaundice of alarming degree, which disappeared after its discontinuation.

Biologic Agents: (*a*) Bacteriophage. No discussion of staphylococcic septicemia would be complete without mention of bacteriophage. It was employed in 12 of these cases: in 2 cases locally and in 2 cases subcutaneously. These 4 cases were fatal. In the 8 other cases it was used intravenously, according to the technic of MacNeal and Frisbee,[10] with unsuccessful results. Death resulted in 6 cases. In the 2 nonfatal cases, bacteriophage had no effect at all in 1, and in the other it was definitely shocking and harmful and produced no effect on the blood culture. Its use was abandoned in each case after two courses, while the patient was still in a critical condition; the eventual recovery was in no way influenced by the administration of bacteriophage.

(*b*) Staphylococcus antitoxin. This was used in 3 cases, with 2 recoveries, but these could not be credited to the antitoxin. With so many strains of staphylococci, it is not likely that a polyvalent antitoxin covering the many groups would contain sufficient units of antitoxin specific for the offending strain attacking the patient to be of any decided value. Indeed, it is doubtful if the offending strain is present in the stock antitoxin in any given case. Such exquisite pain is caused by the intramuscular administration of the antitoxin that one wonders if it is worth the inconvenience and the loss of sleep imposed on the patient. However, in the future there is a possibility that this method of approach to the problem may be of paramount value when individual strains of staphylococci can be isolated and effectively neutralized and specific antitoxins obtained.

(*c*) Staphylococcus toxoid. This was used in 2 cases; 1 case was fatal, and in the other the toxoid was given after recovery had been established, so that its usefulness could not be appraised in this study.

Miscellaneous Forms of Treatment: Roentgen therapy was used in 2 cases and foreign protein therapy in 1 case. The results were questionable.

Constant Watch for Metastatic Foci, with Prompt Eradication by Surgical Treatment Whenever Possible.—The blood stream may be sterilized, and yet if the state of sepsis is continued by a metastatic focus, the blood stream may be reinfected. Of course, metastatic foci are not always accessible; therefore it is not possible to eradicate them in every case (multiple pulmonary abscesses in case 1). In such instances supportive measures offer the only hope. Case 2 shows how effectively bilateral renal abscesses were combated by surgical measures and that recovery would have been impossible in this case without their removal. No amount of surgical treatment is too much until all accessible foci are removed.

PROGNOSIS

From this study and other reported studies of staphylococcic septicemia, the following factors are found to bear on the prognosis of this desperate infection: The possibility of eradicating the primary focus of infection that is feeding the blood stream as well as the possibility of combating the extension of the infection into distant organs and removing metastatic foci influences the prognosis favorably. The sthenic age, young adulthood, as in most diseases, is the most favorable age with respect to combating the disease. Most of the recoveries in this series occurred in this age group. The promptness with which treatment is instituted is important for a favorable outcome. In many cases the disease is not recognized early enough so that measures can be taken to prevent its deadly effects and extension. It is not uncommon for the condition to be treated under a mistaken diagnosis for some time before the true state of affairs is recognized. Pneumonia was the most frequently mistaken diagnosis in this series, and the error can readily be understood when chill, fever and cyanosis and often rales in the chest, with leukocytosis, all of sudden onset, confront the examiner. Lagrippe was a frequent mistaken diagnosis in the cases of osteomyelitis. If the disease can be recognized at the onset and surgical treatment, transfusions and other measures employed to prevent extension, the chances of recovery are greatly enhanced.

Positivity of the result of blood culture is also a factor in the prognosis. The less numerous the colonies of staphylococci in the blood culture, the more favorable the chances for recovery.

The coexistence of other disease states, particularly diabetes mellitus, with staphylococcic septicemia offers a very poor outcome. There were 9 such cases and all were fatal. The extension of the disease to the brain, meninges or heart likewise influences the prognosis unfavorably. The 7 patients with meningitis and the 4 with cardiac toxic changes all died. The very young and the aged do poorly with this infection. The impossibility of eliminating the original source of infection or of prohibiting the extension of the infection also influences the prognosis unfavorably. Delay in treatment may also cost a life.

REPORT OF THREE CASES IN WHICH RECOVERY WAS OBTAINED

CASE 1.—D. M., a man aged 33, was admitted to the Mount Sinai Hospital under the author's care on June 10, 1937, because of a sudden chill and elevation of the temperature to 103 F., secondary to a huge carbuncle on the back. He was toxic, septic and acidotic; the leukocyte count was high and the urine was loaded with casts, albumin, red blood cells, white blood cells and acetone. One hour after entry the carbuncle was decapitated and drained (by Dr. Benjamin Lipshutz); the organism obtained was Staph. aureus haemolyticus. A twenty-four hour blood culture showed Staph. aureus haemolyticus. Repeated daily incisions into the carbuncle for wider drainage, several transfusions, staphylococcus antitoxin and supportive measures failed to halt the advancing infection and downhill course. The results of blood culture increased in positivity, and the general condition was critical. At this point, on June 14, a wide excision of the entire carbuncle and surrounding area into healthy tissue was performed, leaving an open wound down to the ribs measuring 7 by 8 inches (18 by 20 cm.). This seemed to be the only means of removing the source of infection that was feeding the blood stream. A specific bacteriophage was then ready and was used locally and intravenously, after the method of MacNeal and Frisbee. After the sixth injection intravenously, the patient had a violent chill, with rigor, and the temperature reached 106.4 F., followed by vasomotor collapse and shock of alarming degree, with a drop in temperature to 100 F. and a rise to 104 F. in the afternoon. Blood culture the following day showed no change, and the general condition of the patient was poorer. On June 18 signs of involvement of the lower lobe of the right lung were present. The next day bacteriophage therapy was repeated, and after the fifth dose intravenously the shock and collapse reaction were so violent and the effects so weakening, without any measure of improvement clinically or in the state of the bacteremia, that this form of treatment was abandoned. On June 19 empyema of the right side of the chest was discovered and tapped; 150 cc. of purulent fluid was obtained, which yielded Staph. aureus haemolyticus. A roentgenogram of the chest showed pleurisy over the lower lobe of the right lung associated with atelectasis, pneumonitis of the left lung and small areas of consolidation scattered throughout both pulmonary fields. Repeated roentgen examinations of the chest soon disclosed, in addition to these findings, the development of five large metastatic abscesses in the lungs. Sulfanilamide therapy was tried but was discontinued because of the development of hepatitis and jaundice. With repeated immunotransfusions, the administration of gentian violet intravenously and Pregl's iodine solution, supportive measures, and incision and drainage of metastatic abscesses of the skin as they occurred, the clinical condition showed some improvement, and on July 11, thirty-two days after entry, blood culture became sterile for the first time. The sepsis continued, however, owing to the many metastatic foci of suppuration, particularly in the lungs. The temperature ranged from 101 to 104 F. daily. On July 31 the patient experienced sudden pain in the right loin and voided 10 ounces (300 cc.) of nearly pure pus, which yielded Staph. aureus haemolyticus. Undoubtedly, spontaneous rupture of a renal carbuncle into the renal pelvis and discharge through the urinary tract occurred. In a few days the urine was clear, with no pus or organisms. Gradually the pulmonary complications improved, and on August 10 roentgen examination revealed disappearance of the pneumonitis, improvement in the atelectasis and beginning resolution of the five abscesses. On September 10 the temperature was normal for the first time, the patient was asymptomatic and the pulmonary condition was better. On September 26 the patient was discharged improved (afebrile) and had

regained 20 of the 50 pounds (9 of the 22.7 Kg.) which he had lost during his illness. For six weeks he was convalescing at home and doing well, with a gain in weight, when sudden severe pain in the left shoulder and disability of motion, with chills and fever developed. He was readmitted to the hospital on November 16 in a toxic condition. Blood culture was sterile. Surgical drainage (by Dr. M. B. Cooperman) of an acute suppurative subacromial bursitis on the left side yielded Staph. aureus haemolyticus (more than four months after the blood had been sterile). Uneventful recovery followed. He is well and asymptomatic and is working full time today. His weight is greater than it has been at any period of his life.

Comment.—Treatment consisted of effective surgical eradication of the source of infection; removal of metastases when possible; thirteen blood transfusions, of which eleven were immunotransfusions; chemotherapy, and the administration of staphylococcus antitoxin and bacteriophage.

CASE 2.—A. DeM., a 23 year old man, was admitted to the service of Dr. A. I. Rubenstone on March 16, 1937, in a septic, toxic state, suffering from a gluteal abscess of one week's duration. The temperature ranged between 101 and 104 F. The abscess was opened and drained, and the pus yielded Staph. aureus haemolyticus. The blood culture made on entry showed in forty-eight hours Staph. aureus haemolyticus. Roentgen treatment over the abscess, repeated transfusions, gentian violet, Pregl's iodine given intravenously and staphylococcus antitoxin produced no response. The condition was grave. Pulmonary extension was detected clinically. Metastatic abscesses appeared on the toe and shoulder and on incision yielded Staph. aureus haemolyticus. On April 1 a specific bacteriophage was given intravenously, according to the method of MacNeal and Frisbee, with no effect. Thirty-one days after entry, with transfusions given every other day, blood culture became sterile for one week, although sepsis continued; finally, on May 2, the blood became sterile and remained so. Another course of treatment with specific bacteriophage was given, with no reaction. In spite of the sterile condition of the blood stream, sepsis, leukocytosis and anemia continued. Toxic hepatosplenomegaly with jaundice continued for weeks. The condition remained stationary until July 22, when the search for metastatic foci of suppuration was rewarded by definite urographic evidence of a huge abscess of the left kidney. Pyuria, with the recovery of staphylococci from the urine, caused suspicion of the renal condition. Nephrectomy was performed by Dr. M. Muschat; the removed kidney contained two large abscesses in the upper and middle portions, from which Staph. aureus haemolyticus was obtained. The temperature and pyuria disappeared for three weeks, during which time there was remarkable clinical improvement. However, fever and pyuria recurred, and on August 20 a urogram showed a huge abscess in the other kidney. Conservative treatment was elected, but because of increasing sepsis and the downhill clinical course, exploration of the remaining kidney was done on September 8. The perinephric tissues were edematous and adherent and a large abscess in the lower pole was incised and drained, as well as one in the middle pole. Both yielded Staph. aureus haemolyticus. The patient did well immediately after operation, the temperature soon reached normal and he gained strength and weight and soon became asymptomatic. He was discharged on October 3. He is now well and back at work.

Comment.—Treatment consisted of surgical eradication of the focus of origin; effective eradication of the metastatic foci of suppuration, without which life would have been impossible; twenty-four blood transfusions; the administration of staphylococcus antitoxin and bacteriophage; chemotherapy, and irradiation.

CASE 3.—M. G., a 13 year old boy, was admitted to the service of Dr. A. Trasoff on May 1, 1937, because of cough, chill, fever and signs of pneumonic consolidation of the lower lobe of the left lung. The temperature was 105 F., toxicity was marked, a toxic rash covered the body, the leukocyte count was high and the urine was loaded with casts and acetone. There was a fluctuating tender swelling of the right shoulder of two days' duration. Blood culture in twenty-four hours showed Staph. aureus haemolyticus. A roentgenogram did not show acute osteomyelitis of the humerus, but the clinical diagnosis was evident. The high temperature persisted, being sustained at 105 F. Accordingly, incision and drainage of the humerus were performed by Dr. M. B. Cooperman, and pus was obtained which yielded Staph. aureus haemolyticus. After surgical drainage the blood culture became sterile within three days, or five days after entry. Within ten days the patient was afebrile. One metastatic abscess of the skin occurred which promptly responded to incision. The patient was discharged cured twenty-four days after entry.

Comment.—Treatment consisted of surgical eradication of the focus that was feeding the blood stream (this controlled the septicemia), two blood transfusions and the administration of staphylococcus antitoxin and gentian violet intravenously.

SUMMARY

Staphylococcic septicemia is the most deadly of all septicemias. A series of 35 patients, seen over an eight year period, is presented. There were 6 recoveries, 29 fatalities and 16 postmortem examinations. The mortality was 83 per cent, which compares well with the rates reported in the literature.

The incidence; sex; age; source of infection; duration of the disease; laboratory findings; complications noted clinically, as contrasted with complications noted post mortem; treatment, and prognosis are discussed. It is shown that complications occur early in the course of the disease and exist more frequently than can be discovered clinically.

In the light of present knowledge of the disease, with no specific treatment as yet available, surgical eradication of the source of infection, with prompt removal of metastatic foci of suppuration as they occur, plus repeated immunotransfusions, offers the foundation for any successful treatment. Three cases in which recovery was obtained are discussed in detail to emphasize these features of the disease.

CORTICAL NECROSIS OF THE KIDNEY FOLLOWING TONSILLITIS

REPORT OF A CASE

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Bilateral, symmetric necrosis of the renal cortex is a rare condition which during the life of the patient often represents a rather difficult diagnostic problem. Kaufmann [1] described this condition as an extensive necrosis of the cortex of the kidney leading to rapid suppression of the excretion of urine and to death attended by uremic symptoms. Extensive confluent yellowish areas of cortical necrosis are found surrounded by deep red hemorrhagic rims and associated with extensive thromboses of the intrarenal arteries and veins. This lesion has been observed chiefly as a fatal complication of pregnancy, and 86 per cent of the cases reported in the literature fall in this group (Evans and Gilbert [2]). Other etiologic factors, such as tonsillitis, periarteritis nodosa, diphtheria, pulmonary tuberculosis, peritonitis and intravenous injections of camphor, must be considered as extremely rare; they are responsible for the small number of cases in which the condition has occurred in males. Because of the rarity of the condition and the interesting etiologic background, we wish to report briefly the following case.

REPORT OF CASE

A white boy 17 years of age entered the University Hospital on Jan. 10, 1938, with pain and tenderness in the lumbar region and swelling of the feet and ankles, face and right forearm. This condition had developed slowly after a prolonged attack of tonsillitis one month previously. The history was negative with regard to previous diseases, and the patient had been in perfect health until the time of the initial illness.

Examination.—The patient was rather emaciated but did not appear acutely ill. The tonsils were small and contained deep crypts. The blood pressure was 130

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1. Kaufmann, E.: Pathology for Students and Practitioners, Philadelphia, P. Blakiston's Son & Co., 1929, p. 1310.

2. Evans, N., and Gilbert, E. W.: Symmetrical Cortical Necrosis of the Kidneys, Am. J. Path. **12**:553-560, 1936.

systolic and 80 diastolic. The heart was moderately enlarged to the left, and a soft systolic murmur was present over the apex. There was muscular tenderness over both kidneys, but no edema of the feet or ankles could be observed during the patient's stay in the hospital. Examination of the urine showed a specific gravity of 1.020 and an albumin content of 300 mg.; in the microscopic examination of the sediment about 70 red blood cells and 30 white blood cells could be observed per high power field, with numerous granular and cellular casts. Examination of the blood showed 2,040,000 red cells and a hemoglobin content of 50 per cent. The leukocyte count was 35,000, with 68 per cent neutrophilic leukocytes and 17 per cent juvenile leukocytes. The platelet count was 607,700, and there were 4 per cent reticulocytes. The renal function test with phenolsulfonphthalein revealed an excretion of only 55 per cent of the dye in three hours. The concentration-dilution test showed moderate disturbance of renal function. The blood urea clearance at the time of the patient's admission was 48.19 per cent. The albumin-globulin ratio of the blood serum was 3.2 : 3.3. The blood cholesterol was 153.8 mg. per hundred cubic centimeters. Cultures of the blood were negative. The electrocardiographic examination showed a slight defect of the intraventricular conduction. The roentgen examination of the chest showed a diffuse dense area in each pulmonary field, which was interpreted as indicating possible pneumonic infiltration or severe passive congestion. The serologic tests for syphilis were negative. At admission there was marked oliguria, which lasted for three days but disappeared suddenly.

Course.—With rest, an antinephritic diet and general supportive treatment the patient improved greatly. The nonprotein nitrogen level of the blood sank from 60 mg. per hundred cubic centimeters to 30 mg. The patient was discharged on the thirty-fourth hospital day.

One week after having been discharged the patient was seized by an attack of acute dyspnea and hemoptysis, and he was readmitted to the hospital on March 4. At this time the blood pressure was 160 systolic and 130 diastolic. Coarse rales were audible over both lungs. The heart showed a gallop rhythm and a blowing first sound at the apex. There was tenderness over both kidneys. There was slight pitting edema over the ankles and sacrum. Examination of the urine showed a specific gravity of 1.023 and 200 mg. of albumin. The reaction for Bence Jones protein was strongly positive. The microscopic examination of the sediment showed 8 red blood cells and 12 white blood cells per high power field with numerous hyaline and erythrocyte casts. The examination of the blood showed an erythrocyte count of 2,950,000 and a hemoglobin content of 50 per cent. The white blood cells numbered 45,640, with 74 per cent neutrophilic leukocytes and 6 per cent juvenile forms. The phenolsulfonphthalein test for renal function revealed an excretion of only 35 per cent of the dye in two hours, and a concentration test showed definitely disturbed renal function. An intravenous pyelogram showed anatomically normal kidneys. The sedimentation rate of the red blood cells was greatly increased. The electrocardiographic examination showed definite evidence of myocardial damage. The patient was placed again on a high protein and saft-free diet with supportive treatment and restriction of fluids. His temperature showed moderate elevation. The output of urine suddenly became markedly decreased; the patient started to vomit; diarrhea developed, and he became somnolent. Examination of his eyegrounds showed the presence of retinal hemorrhages. Two days before death he had complete anuria and brief attacks of convulsions, followed by deep coma. He died on the eighteenth day in the hospital.

Autopsy.—The body was well developed but poorly nourished. Scattered over the face were numerous purplish spots, 1 to 3 mm. in diameter. The back and the tip of the nose showed purplish discoloration. The skin and mucous membranes appeared slightly anemic. The hands, the forearms, the lower parts of the legs and the feet showed a moderate degree of pitting edema. The nails were deeply cyanotic. There were scattered purplish spots over the left forearm. Larger areas of subcutaneous hemorrhage were present over the thighs.

The heart weighed 450 Gm. The left ventricle showed hypertrophy and moderate dilatation. The pericardium and myocardium showed no pathologic changes. The endocardium showed a few antemortem thrombi located between and behind the trabeculae of the ventricles. An antemortem thrombus was also observed in the left auricular appendage. Both lungs were voluminous and well expanded. The pleura presented many confluent and discrete petechial hemorrhages. The lung tissue showed numerous moderate-sized, recent hemorrhagic infarcts. There also were considerable edema and passive congestion in the lower lobes. The spleen weighed 200 Gm. and was soft. There was a diffuse increase in the pulp substance. The liver weighed 1,600 Gm. Irregular congestion was present, which gave the organ a reddish brown mottled appearance. The esophagus contained blackish material, which also stained its wall. The mucous membrane of the stomach showed numerous ecchymoses and some irregular areas of atrophy. The ileum and the colon showed circumscribed areas of congestion. The kidneys were enlarged and weighed 210 Gm. each. The capsules stripped with some difficulty. The surface of the kidney showed irregular mottling, with confluent areas of yellowish gray most prominent. Some of these areas were surrounded by deep reddish lines of demarcation, while others seemed to be surrounded by small zones of normal kidney tissue. The cut surfaces of the kidneys revealed a marked yellowish red mottling of the cortical zone, with the yellowish areas by far in predominance. The medullary tissue appeared normal except for some hemorrhagic streaks in the subcortical regions. The mucous membrane of the kidney pelvis and the ureters were normal. The urinary bladder was well contracted and contained a few cubic centimeters of cloudy urine. One testicle showed a large diffuse parenchymatous hemorrhage. Section of the brain revealed petechial hemorrhages in the region of the thalamus and in the choroid plexus of the lateral ventricles.

Microscopic examination of the heart revealed moderate hypertrophy of the heart muscle. Some of the muscle fibers showed marked fatty degeneration. A few of the smaller coronary vessels were dilated, their lumens filled with thrombotic material containing polymorphonuclear leukocytes, erythrocytes and an amorphous granular material. Sections of the lungs showed large areas of hemorrhagic infarction surrounded by zones of pneumonic infiltration. The pulmonary vessels appeared dilated. Some of them showed hyalinization of the wall, while others were filled with small thrombi. In the infarcted areas large colonies of cocci could be recognized. The spleen showed moderate hyperplasia of the pulp with an increase of polymorphonuclear leukocytes. A few small splenic arteries showed partial hyalinization of the walls with thrombus formation. Sections through the lymph nodes showed marked congestion of vessels and increased desquamation of the endothelium of the sinuses. The liver showed moderate parenchymatous degeneration of the hepatic cells. The dark reddish areas of liver tissue showed marked acute congestion with destruction of the center of the hepatic lobule. The brownish parts of the liver showed no congestion of the capillaries and only moderate fatty degeneration in the center of the hepatic lobule.

The vessels of the liver did not show any pathologic changes. Sections of the esophagus showed extensive superficial necrosis of the mucous membrane with phlegmonous infiltration of the submucous layer and hemorrhagic imbibition of the necrotic area. Some of the vessels in the submucous region appeared to be thrombosed. The adrenal gland showed lipoid depletion of the cortex, moderate passive congestion, an occasional small focus of necrosis and minute areas of hemorrhage. Sections of the skin and the subcutaneous tissue showed small petechial hemorrhages. Sections of the brain showed numerous thrombi in the

Fig. 1.—Cut surface of the kidney, showing the gray areas of cortical necrosis.

smaller vessels with extravasation of blood into the perivascular lymph spaces. The thrombi were principally hyaline and amorphous in nature. The wall of the vessel seemed sometimes to be infiltrated with leukocytes.

Sections of the kidneys showed a change resembling a diffuse and irregular infarction of the entire cortical zone. Some glomeruli were enlarged and filled with blood; others were small and necrotic. Occasionally some fibrosis of the capsule could be observed, indicating previous glomerular damage. The afferent vessels were greatly dilated and showed hyalinized thrombi, which in some cases continued into the loops of the glomerular capillaries. The walls of the afferent

capillaries were often hyalinized or necrotic. A few noninfarcted glomeruli showed an increase in cells suggestive of a proliferative type of glomerular nephritis, while others were normal. The tubular epithelium showed extensive

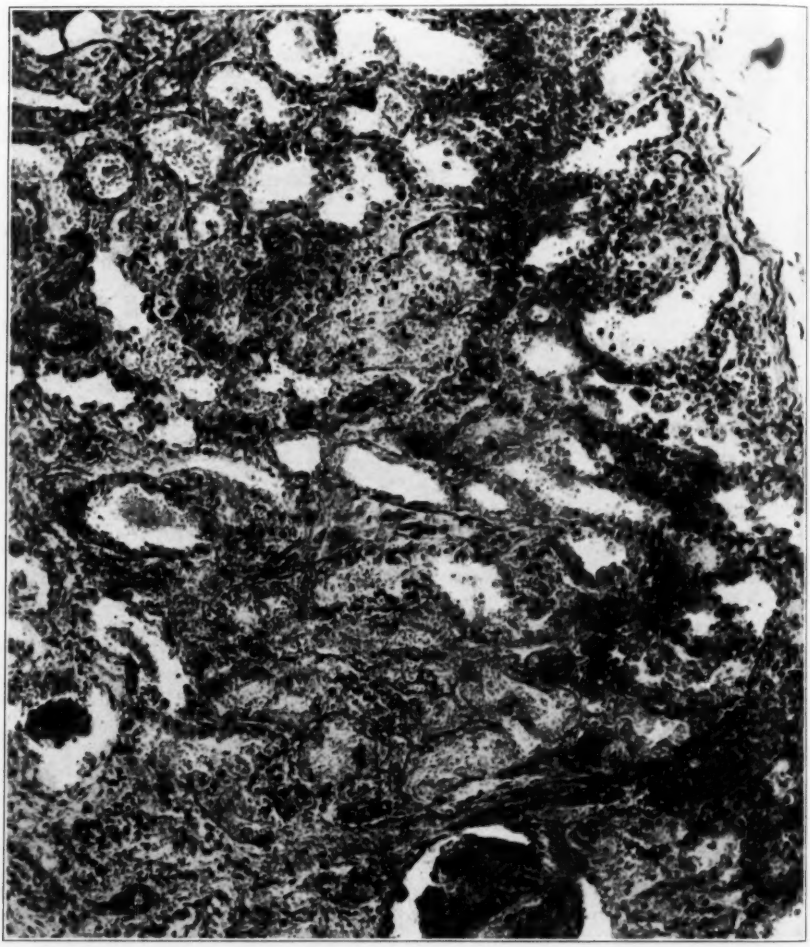

Fig. 2.—Coagulation necrosis of the cortex of the kidney surrounded by a wall of leukocytes; hematoxylin and eosin stain; × 120.

necrosis with marked desquamation and an amorphous pink-staining material filling the lumens. The interlobular arteries and veins were greatly dilated and showed partial or complete hyalinization of the walls. The lumen was filled with thrombi consisting of an amorphous granular material, red blood cells and

leukocytes. The arterial thrombi were predominantly hyaline or amorphous in character, while the venous thrombi were more cellular. Diffuse imbibition of the thrombus as well as of parts of the vascular wall with fibrosis could be demonstrated with the method of Weigert. With Unna's stain a large amount of

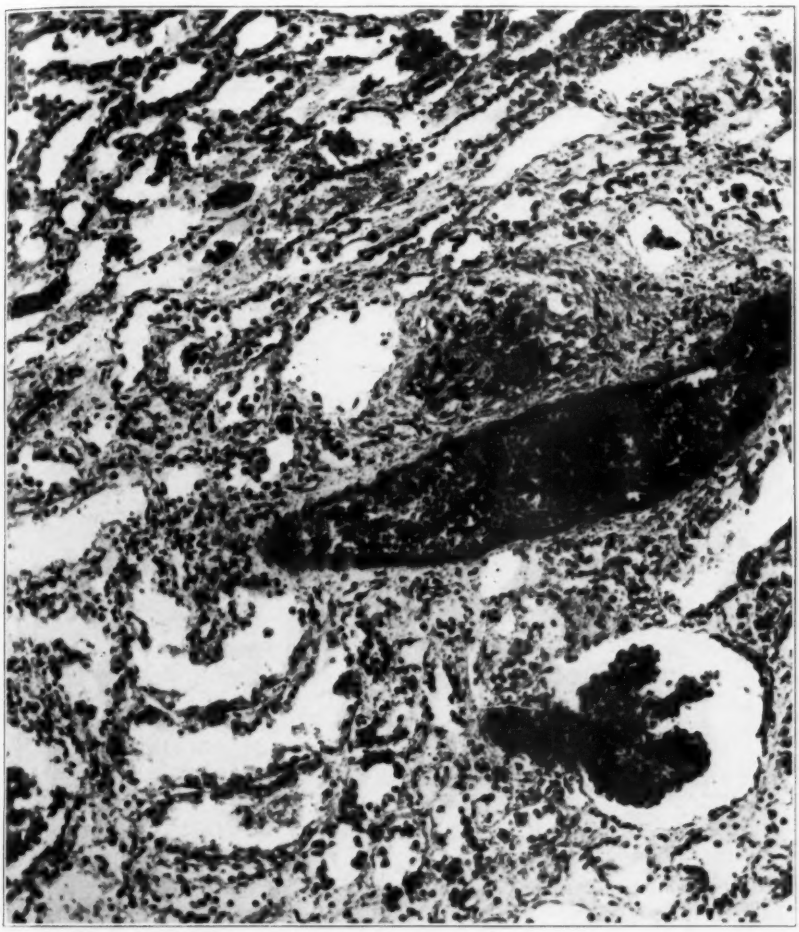

Fig. 3.—Thrombus formation in the interlobular vessels; hematoxylin and eosin stain; × 120.

hyalin could be demonstrated in the thrombi of the afferent vessels and in the loops of the glomeruli. The interstitial tissue of the kidney appeared edematous and slightly infiltrated with leukocytes and round cells. There was a dense zone

of leukocytes just beneath the capsule forming a line of demarcation around the infarcted tissue. The medulla showed moderate congestion of blood vessels but no evidence of tissue necrosis.

COMMENT

Cortical necrosis of the kidney is clinically characterized by its rapid and relatively symptomless course (Davidson and Turner,[3] Torrens[4]). Its most important symptoms are nocturia, oliguria and, finally anuria (Manley and Kliman[5]). The last is without doubt the most striking feature of the disease, although it is not complete in most cases (Rolleston,[6] Wordley[7]). Convulsions, headache, impaired vision, edema and diarrhea may be regarded as terminal symptoms indicating an advanced stage of uremia (Ash[8]). In the case of Bradford and Lawrence[9] the patient remained lucid until his death. Pain and tenderness in the region of the kidneys were mentioned by Manley and Kliman,[5] while in the cases of Bamforth[10] and von Zalka[11] abdominal pain preceded the anuria. The small quantity of urine excreted contains a large amount of albumin, red blood cells and leukocytes, with numerous granular and hyaline casts. The appearance of Bence Jones protein in our case must be recorded as unusual. The leukocyte count of the blood is usually greatly elevated (Manley and Kliman[5]); in our case the number of white cells rose to 46,000. The blood pressure is variable, ranging from normal levels to a systolic high of 200 mm. of mercury (Evans and Gilbert[2]). The temperature may be elevated, especially in the presence of bacterial infection, but it often becomes subnormal in the later stages

3. Davidson, J., and Turner, R. L.: Bilateral Cortical Necrosis of the Kidneys: A Clinical and Pathological Report of Four Cases, Edinburgh M. J. **37**: 101 (July) 1930.

4. Torrens, J. A.: Massive Infarction of the Renal Cortex, Lancet **1**:99, 1911.

5. Manley, J. R., and Kliman, F. E.: Cortical Necrosis of the Kidneys in Pregnancy, Am. J. Obst. & Gynec. **14**:802-806, 1927.

6. Rolleston, H. D.: Symmetrical Necrosis of the Cortex of the Kidneys, Associated with Suppression of Urine in Women Shortly After Delivery, Lancet **2**:1173-1175, 1913.

7. Wordley, E.: A Case of Cortical Necrosis of the Kidney with Polyarteritis Acuta Nodosa, Lancet **2**:927-928, 1923.

8. Ash, J. E.: Bilateral Cortical Necrosis of the Kidneys, Am. J. M. Sc. **185**: 71-86, 1933.

9. Bradford, J. R., and Lawrence, T. W. P.: Endarteritis of the Renal Arteries, Causing Necrosis of the Entire Cortex of Both Kidneys, J. Path. & Bact. **5**:195, 1898.

10. Bamforth, J.: A Case of Symmetrical Cortical Necrosis of the Kidneys Occurring in an Adult Man, J. Path. & Bact. **26**:40-45, 1923.

11. von Zalka, E.: Ueber symmetrische Rindennekrose der Niere, Virchows Arch. f. path. Anat. **290**:53-70, 1933.

of the disease (Apert and Bach [12]). Chemical studies of the blood reveal in all cases a rapid rise in the retention of nitrogenous products, which can often be demonstrated in hourly intervals (Dalrymple [13]). Retinal edema (Hirst [14]) or a cotton wool appearance of the disks (Carson and Rockwood [15]) is present in a large number of cases, often associated with capillary hemorrhages, as we observed. The duration of the disease depends on the degree of suppression of urination. If it is complete, death may be observed as early as twenty-four hours after its onset (Torrens [4]), while in cases of incomplete anuria a duration of from fourteen to twenty-one days has been observed. Gibberd [16] published reports of 2 cases in which the patient recovered from anuria lasting nine and ten days, respectively, the nonprotein nitrogen level of the blood returning to normal a few days after cessation of the anuria. In such cases the diagnosis of cortical necrosis was disputed by Scriver and Oertel,[17] who expressed the belief that the mere fact of recovery speaks against the presence of this renal lesion. Death usually occurs after the sudden appearance of severe uremic symptoms, accompanied by coma and convulsive seizures.

At autopsy the kidneys usually are slightly enlarged, with a mottled yellowish gray and dark red or violet red surface (Juhel-Rénoy [18]). The greater part of the cortex shows a whitish yellow color characteristic of ischemic necrosis and is surrounded by thin dark red serrated lines of demarcation (Glynn and Briggs [19]). The renal pyramids are usually dark red and of normal texture. Subcapsular hemorrhages have been described by Jardine and Teacher.[20] Grossly recognizable throm-

12. Apert, M. E., and Bach, E.: Insuffisance rénale aiguë chez un tuberculeux: Necrobiose frappant exclusivement toute l'entendue de la substance corticale des deux reins, Bull. et mém. Soc. méd. d. hôp de Paris **52**:471-476, 1928.

13. Dalrymple, S. C.: Thrombosis of the Interlobular Arteries of the Kidneys in Pregnancy, New England J. Med. **203**:160-162, 1930.

14. Hirst, J. C.: Suppression of the Urine in Connection with Pregnancy, Am. J. Obst. & Gynec. **12**:673-683, 1926.

15. Carson, W. J., and Rockwood, R.: Symmetrical Cortical Necrosis of the Kidneys in Pregnancy, Arch. Path. **1**:889-893 (June) 1926.

16. Gibberd, G. F.: Symmetrical Cortical Necrosis of the Kidneys, J. Obst. & Gynaec. Brit. Emp. **43**:60-73, 1936.

17. Scriver, W. de M., and Oertel, H.: Necrotic Sequestration of the Kidneys in Pregnancy (Symmetrical Cortical Necrosis), J. Path. & Bact. **33**:1071-1094, 1930.

18. Juhel-Rénoy, E.: De l'anurie précoce scarlatineuse, Arch. gén. de méd. **17**:385-410, 1886.

19. Glynn, E. E., and Briggs, M. B.: Symmetrical Cortical Necrosis of the Kidney in Pregnancy, J. Path. & Bact. **19**:321-332, 1915.

20. Jardine, R., and Teacher, J. H.: Two Cases of Symmetrical Necrosis of the Cortex of the Kidneys Associated with Puerperal Eclampsia and Suppression of Urine, J. Path. & Bact. **15**:137-146, 1910.

bosis of the larger renal vessels was present in the case of Rolleston.[6] In the microscopic examination the characteristic changes are confined to the cortical zone and are remarkable for their uniformity. The lesion resembles an anemic infarct except for its irregular outline and the marked engorgement of the vessels in the necrotic area (Ash[8]). A small strip of subcapsular cortical tissue is often intact and separated from the necrotic area by dense zones of leukocytes (Bamforth[10]). Similar zones of nonnecrotic tissue, often filled with small hemorrhages, may be observed just above the medulla. In our case the necrotic areas had a distinctly confluent character, and small islands of nonnecrotic kidney tissue could be seen between the areas of infarction. The wall of leukocytes demarcating the necrotic tissue was absent in some places. The glomerular changes in this condition may be manifold. Some glomeruli show hemorrhagic infarction, while others appear collapsed and necrotic. Hyaline thrombi could be observed by us in some afferent vessels, while Juhel-Rénoy[18] and Hirst[14] reported the occurrence of fibrin thrombi in the loops of the glomeruli. Evidence of chronic glomerular nephritis was present in the case of Glynn and Briggs,[19] and also in our case glomeruli not involved in the necrotic process showed some endothelial proliferation with fibrosis. The presence of eosinophilic cells in the tufts was mentioned by zu Jeddeloh;[21] an increase of intravascular fat in the glomerular tufts was described by Warner and Hibbitts,[22] and the presence of microbes in the glomerular loops was stressed by Juhel-Rénoy. The tubular epithelium in the necrotic cortical areas shows all degrees of cloudy swelling, fatty degeneration and coagulation necrosis. The outline of the structure of the tubules is usually preserved. The lumen may be dilated and filled with amorphous casts containing large amounts of fibrin (zu Jeddeloh[21]). The tubular epithelium in the capsular zone has a marked tendency to cloudy swelling (Bradford and Lawrence[9]). The collecting tubules in the medulla may show slight degenerative changes, the lumen containing albuminous casts. The lack of necrosis was explained by Scriver and Oertel[17] by an increased anastomosis of the vessels therein. The most striking feature of the lesion is without doubt the appearance of massive thrombi in the vessels of the cortical zone. The interlobular arteries and veins as well as their branches are plugged by thrombotic material consisting of amorphous material, leukocytes and erythrocytes. In our case the venous thrombi were more cellular, while the arteries were usually filled with homogeneous hyaline material. The presence of a large amount of platelets in these thrombi

21. zu Jeddeloh, B.: Eine seltene Form akuter tödlicher Nierenerkrankung nach Fehlgeburt, Virchows Arch. f. path. Anat. **286**:389-408, 1932.

22. Warner, C. G., and Hibbitts, J. T.: Symmetrical Cortical Necrosis of the Kidneys in Pregnancy, Am. J. Obst. & Gynec. **23**:875-881, 1932.

was described by Manley and Kliman.[6] The wall of the vessel usually takes on a hyaline, or even necrotic, appearance (zu Jeddeloh[21]), and sometimes endarteritis is present, which, however, is not the most impressive part of the pathologic picture (Lloyd[23]). In some places the elastic fibers of the vessels are completely destroyed, and small hemorrhages can be seen in the perivascular zones.

In Bell's[24] excellent discussion of clinical acute nephritis, two groups of lesions are listed which must be differentiated from widespread primary thrombosis of small renal arteries. Both represent subtypes of acute glomerular nephritis, namely, the type associated with thrombosis of glomerular capillaries and the type associated with thrombosis of afferent arterioles. In none of these types, however, will actual tissue necrosis involving large areas of cortical zones occur, nor is the presence of thrombotic masses of the larger vessels observed.

The cause of the thrombosis of the renal vessels is still under dispute. Since damage to the endothelium by toxins is one of the commonest causes of thrombosis (Glynn and Briggs[19]), such injury to the vessels could well be expostulated as the primary factor in this lesion. The theory of Juhel-Rénoy that organisms may be the primary cause of plugging of the lumen of the vessel with secondary thrombus formation can be regarded as obsolete. The histologic examination in our case seemed to support well the theory of primary damage to the wall of the vessel as the cause of thrombus formation since similar changes were observed also in the spleen, lung, heart and brain, leading to thrombosis with infarction of the lung and encephalomalacia. The predominant involvement of the renal vessels in the thrombotic process may be partly explained in our case by increased blood stasis in the interlobular arteries caused by the existing glomerular damage.

There is also considerable dispute as to the importance of these thrombi in the causation of the cortical necrosis. De Navasquez[25] expressed the belief that thrombosis is conspicuous for its extreme infrequency, and that it is only a terminal symptom, representing aggregated masses of blood cells consequent to stasis. In 14 of 44 cases collected by Ash[8] no thrombi were reported. Also, Dalrymple[13] stated that the thrombosis in the vessel is secondary to necrosis. Against this argument we may cite again the observations made in our case, in which thrombi associated with changes in the vascular walls caused infarction in the lungs and the brain, while they were observed without tissue

23. Lloyd, H. C.: Necrosis of the Entire Renal Cortex of Both Kidneys, Lancet **1**:156, 1906.

24. Bell, E. T.: The Early Stages of Glomerulonephritis, Am. J. Path. **12**: 801-824, 1936.

25. De Navasquez, S.: The Histology and Pathogenesis of Bilateral Cortical Necrosis of the Kidney in Pregnancy, J. Path. & Bact. **41**:385-396, 1935.

necrosis in the spleen and the heart. They cannot be regarded, therefore, as sequelae of the tissue necrosis.

With regard to the angiospastic theory of Ash [8] and Schmorl and Beneke,[26] we may emphasize that the marked dilatation of the obstructed vessels rather should suggest toxic vasoparalysis, as assumed by Scriver and Oertel. This again, would be an additional factor in promoting thrombus formation.

SUMMARY

A case of symmetric cortical necrosis of the kidneys following tonsillitis is reported. The microscopic picture revealed evidence of existing glomerulonephritis on which the ischemic necrotic process was superimposed. The interlobular arteries and veins and their smaller branches showed hyalinization of the wall with thrombus formation. Similar, but less marked, changes could be observed also in the vessels of the spleen, heart, lungs and brain. The importance of damage to the wall of the vessel by circulating toxins in production of the thrombi with subsequent tissue infarction is discussed.

26. Schmorl and Beneke, cited by Kaufmann.[1]

EXCRETION OF ASCORBIC ACID IN RELATION TO SATURATION AND UTILIZATION

WITH SOME DIAGNOSTIC IMPLICATIONS

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In the past few years numerous reports have appeared in the literature dealing with the metabolism of ascorbic acid in man. These studies made use of the Harris-Ray [1] modification of the Tillman method of titrating for this substance in the urine and the Farmer-Abt [2] method for its detection in blood plasma. Several general conceptions were evolved from these studies:

1. Ascorbic acid is excreted in the urine in its reduced state in almost all persons, the exact quantity depending on the amount of intake, but the minimal normal amount is considered to be around 20 mg. per twenty-four hours.[3]

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1. Birch, T. W.; Harris, L. J., and Ray, S. N.: A Micro-Chemical Method for Determining the Hexuronic Acid (Vitamin C) Content of Foodstuffs, etc., Biochem. J. **27**:590, 1933.

2. Farmer, C. J., and Abt, A. F.: Ascorbic Acid Content of Blood, Proc. Soc. Exper. Biol. & Med. **32**:1625, 1935.

3. (*a*) Youmans, J. B.; Corlette, M. B.; Akeroid, J. H., and Frank, H.: Studies of Vitamin C Excretion and Saturation, Am. J. M. Sc. **191**:319, 1936; (*b*) A Clinical Study of Vitamin C Excretion, South. M. J. **29**:37, 1936. (*c*) Drigalski, W. V.: Ueber Vitamin C im Urin von Gesunden und Kranken, Klin. Wchnschr. **14**:338, 1935. (*d*) Hawley, E. E.; Stephens, D. J., and Anderson, G.: The Excretion of Vitamin C in Normal Individuals Following a Comparable Quantitative Administration in the Form of Orange Juice and Cevitamic Acid by Mouth and Cevitamic Acid Intravenously, J. Nutrition **1**:135, 1936. (*e*) Schroeder H.: Ueber die Ausscheidung der Ascorbinsäure in gesunden und kranken Organismus, Klin. Wchnschr. **14**:484, 1935. (*f*) Finkle, P.: Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, J. Clin. Investigation **16**:587, 1937. (*g*) Van Eekelen, M.; Emmerie, A.; Josephy, B., and Wolf, L. K.: Ueber Vitamin C in Körperflüssigkeit, Klin. Wchnschr. **13**:564, 1934. (*h*) Harris, L. J., and Ray, S. N.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, Lancet **1**:71, 1935. (*i*) Harris, L. J.; Ray, S. N., and Ward, A.: The Excretion of Vitamin C in Human Urine and Its Dependence on Dietary Intake, Biochem. J. **27**:2011, 1933. (*j*) Johnson, S. N., and Zilva, S. S.: The Urinary Excretion of Ascorbic and Dehydroascorbic Acid in Man, ibid. **28**:1393, 1934.

2. Reduced ascorbic acid is found in the blood stream of normally nourished persons; the concentration of this is 0.7 to 0.9 mg. per hundred cubic centimeters of plasma or higher.[4]

3. Ascorbic acid is stored in almost all of the tissues of the body,[5] and when these body stores are filled to capacity the state has been referred to as "saturation."

Thus, if a person excretes much less than 20 mg. per twenty-four hours, it has been regarded as a sign of a deficient intake of the vitamin, but the degree of deficiency cannot be surmised from this alone. The concentration in the blood if it is in the very low levels or the very high levels is a fairly good index of the immediate state of vitamin C nutrition, but if it is in the borderline levels it is more uncertain. In this respect the "saturation test" is much more helpful. If a fairly large dose, consisting of several hundred milligrams of ascorbic acid, is administered to a normal person, a sharp rise in the amount excreted in the urine occurs within several hours,[6] and in twenty-four hours normal persons will have excreted 30 per cent or more of a 600 mg. test dose.[3ab] If such a large dose is given to a person who is deficient in the vitamin, no rise in the amount excreted will take place until the body stores are beginning to be filled, and this will take longer if the body stores are more completely depleted. It has also been demonstrated that normal persons will excrete 75 per cent or more of this intake when the body stores have been completely filled or saturated,[3a, b, j] although unexplained fluctuations have been noted.[6a] Another test[7] for vitamin C saturation proposed consists of administering intravenously 100 mg. of ascorbic acid and examining the postinjection urinary excretion of the vitamin.

It is generally assumed that low urinary excretion and low blood concentration of ascorbic acid is indicative of a deficient intake. However, it has been demonstrated that at least in febrile patients there is a decreased excretion of ascorbic acid which is not wholly dependent on

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4. (*a*) Greenberg, L. D.; Rinehart, J. J., and Phatak, N. M.: Studies on Reduced Ascorbic Acid Content of Blood Plasma, Proc. Soc. Exper. Biol. & Med. **35**:135, 1936. (*b*) Taylor, F. H. L.; Chase, D., and Faulkner, J. M.: Estimation of Reduced Cevitamic Acid in Blood, Serum, and Plasma, Biochem. J. **30**:1119, 1936. (*c*) Farmer and Abt.[2]

5. King, C. G.: Vitamin C, Ascorbic Acid, Physiol. Rev. **16**:238, 1936.

6. Abbasy, M. A.; Harris, L. J.; Ray, S. N., and Marrack, J. R.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, Lancet **2**:1399, 1935. Harris, Ray and Ward.[3i] Johnson and Zilva.[3j]

7. Ralli, E. P.; Friedman, G. J., and Kaslow, M.: An Excretory Test for Vitamin C Deficiency and Subnutrition, Proc. Soc. Exper. Biol. & Med. **36**:52, 1937. Finkle.[3f]

a decreased intake.[8] We were interested in finding whether there are anomalies of utilization and storage in other clinical conditions, as determined by the rate of saturation, excretion and rise in blood concentration.

EXPERIMENTAL PROCEDURE

Each patient saved all the urine of each twenty-four hours in a stoppered amber bottle. The specimen was kept in the refrigerator and preserved with twice-normal sulfuric acid, 10 per cent by volume, and then titrated with 2, 6-dichlorophenolindophenol. This acid was chosen because of its greater efficiency in preventing oxidation.[9]

The blood was drawn in the morning before any vitamin C was taken; hence it was a fasting specimen even though the patient might have taken some other foods. Determinations of the vitamin in the blood were made at frequent intervals but not daily. The method used was a modification of the one described by Farmer and Abt.[2] About 7 cc. of blood was oxalated and centrifuged, 2 cc. of the supernatant serum was removed, and to it were added 4 cc. of distilled water, 2 cc. of 5 per cent sodium tungstate and 2 cc. of third-normal sulfuric acid; this was again centrifuged, and 4 cc. of the supernatant fluid was used for titration instead of 2 cc. as recommended by Farmer and Abt. This was titrated immediately with sodium 2, 6-dichlorobenzenoneindophenol, but while the recommended dilution of this dye is about 1:5,000, we used a dilution of 1:20,000. This reduced the percentage of error, since a greater amount of solution was required to produce the end point. In a portion of the experiment we further modified this technic by the addition of potassium cyanide (KCN) to the oxalated blood. This, according to Pijoan and Klemperer,[10] prevents the oxidation of the ascorbic acid, and higher values are obtained. We also found this to be the case. The values obtained by the use of this modification are distinguished by the addition of "KCN."

The patients and controls were first on ward diets; then they were put on vitamin C-free diets, and 400 mg. of ascorbic acid was administered daily in tablet form, divided into two doses. The initial level of the ascorbic acid excreted was noted, along with the rate of the rise in excretion, the rapidity with which saturation was attained and the changes in the plasma concentration of ascorbic acid. The excretion of 75 per cent or more of the 400 mg. dose was considered by us as a sign of saturation.

SCURVY

Chick and Hume [11] in 1917 and Cohen and Mandel [12] in 1918 furnished experimental proof of the correctness of the old theory that

8. Abbasy, M. A.; Harris, L. J., and Hill, N. G.: Vitamin C and Infection: Excretion of Vitamin C in Osteomyelitis, Lancet **2**:177, 1937. Bullowa, J. G. M.; Rothstein, I. A.; Ratish, H. D., and Harde, E.: Cevitamic Acid Excretion in Pneumonia and Some Other Pathological Conditions, Proc. Soc. Exper. Biol. & Med. **34**:1, 1936. Harris, L. J.; Passmore, R., and Pagel, W.: Influence of Infection on Vitamin C Content of Tissues of Animals, Lancet **2**:183, 1937.

9. Youmans, Corlette, Akeroid and Frank.[3a, b] Johnson Zilva.[3j]

10. Pijoan, M., and Klemperer, F.: Determination of Blood Ascorbic Acid, J. Clin. Investigation **16**:443, 1937.

11. Chick, H., and Hume, E. W.: The Distribution Among Foodstuffs (Especially Those Suitable for Rationing of Armies) of the Substances Required for the Prevention of Beriberi and Scurvy, J. Roy. Army M. Corps **29**:121, 1917.

(Footnotes continued on next page)

scurvy is due to deficiency of a substance found in fresh fruits and vegetables. This substance is now known to be ascorbic acid. Until recently the diagnosis of scurvy was based on three factors: (1) a history which demonstrated deficiency of vitamin C–containing foods in the diet, (2) symptoms and findings in reference to the gums, hemorrhages, fragility of the superficial and deep capillaries, and subperiosteal hemorrhages in children and (3) therapeutic results. Any or all of these may be erroneous or unreliable for a positive diagnosis. An accurate or reliable history in reference to consumption of vitamin C–containing foods may be difficult to obtain. Often it is difficult to get an accurate account of a patient's diet for a long period. Short periods of consumption of foods rich in vitamin C may be overlooked, and yet during such periods sufficient storage of ascorbic acid may have occurred to make subsequent deficiency harmless. Likewise, vitamin C–containing foods may be consumed but not utilized by reason of diarrhea, vomiting or destruction by intestinal bacteria.[13] Also, certain foods vary greatly in their content of this vitamin, depending on the manner of their use, storage and distribution. Among these may be mentioned milk, which has considerable vitamin C originally but loses it rapidly on pasteurization and exposure to light and air; dried fruits, which contain a negligible amount of vitamin C, and fresh fruits, the processing of which entails a considerable loss of vitamin C.[14]

The symptomatic picture may be incomplete and insufficient for certain diagnosis. The gum symptoms are absent in edentulous persons and in persons with mild deficiency. The subcutaneous and other hemorrhages may be due to purpura of other causation, and the capillary fragility test may be negative in a patient with true scurvy or positive in a nonscorbutic person.[15]

The therapeutic test of giving a vitamin C–rich diet may be objected to in that other substances are supplied in this diet which may be responsible for the improvement rather than vitamin C. Coincidental spontaneous remission of a condition other than scurvy must be considered.

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12. Cohen, B., and Mandel, L. B.: Experimental Scurvy of the Guinea Pig in Relation to Diet, J. Biol. Chem. **35**:425, 1918.

13. Marin, P.: Scorbuto da distruzione batterica intestinale di vitamina C? Minerva med. **2**:25, 1936.

14. Kahn, S. K.: Influence of Certain Agents on the Lability of the "Reducing Factor" (Vitamin C) in Milk, Nature, London **132**:446, 1933; Lability of the "Reducing Factor" (Vitamin C) in Milk, ibid. **132**:64, 1933. King.[5]

15. Armentano, L.: Hämorrhagische Diathese und Vitamin C.: Der Nachweis der Hypovitaminosen aus dem Harn, Ztschr. f. klin. Med. **129**:685, 1936. Baumann, T., and Rappolt, L.: Untersuchungen zum C–Vitaminstoffwechsel: Untersuchungen über die Beziehungen der Festigkeit der Hautkapillaren (Kapillarresistenz) zu dem Sättigungsgrad des Organismus an C-Vitamin, Ztschr. f. Vitaminforsch. **6**:43, 1937.

Recent studies on vitamin C excretion and saturation throw some additional light on the subject. However, all these reports dwell on the quantitative difference between scorbutic and nonscorbutic persons in relation to vitamin C, and most of the studies of scurvy in adults deal only with the urinary excretion of the vitamin.

A case of scurvy in an adult was reported by Wood [16] in which there was no excretion of vitamin C in the urine, and even after the patient received 1,000 mg. of ascorbic acid by mouth only 1.7 mg. was excreted. In Schultzer's [17] 3 cases and in the case reported by Archer and Graham [18] the initial amounts excreted were only slightly below the amounts excreted by the controls. The observers administered the vitamin both by mouth and by vein in varying amounts and both in the form of orange juice and in that of pure ascorbic acid. Their patients showed difficulty in saturation; i. e., it required prolonged high vitamin feeding to produce saturation. Archer and Graham noted that their patient excreted only 51 per cent of the intake after three weeks, while their controls excreted 75 per cent of the intake after several days to one week. Nisenson and Cohen [19] recently reported a case of scurvy in an adult whose initial excretion was 1.75 mg. in twenty-four hours. A test dose of 600 mg. produced no rise. Then 280 mg. and 330 mg. were given daily for eight days each. The excretion remained around 6.5 mg. until the twelfth day, when a perceptible rise occurred and higher levels were maintained. On the tenth day of this treatment the patient appeared entirely well. However, the tourniquet test was still slightly positive on the eighteenth day.

The studies of the ascorbic acid in the blood were done chiefly on infants with scurvy. One of the first reports was by Abt and Epstein,[20] who gave exceptionally high values for scorbutic infants. One patient had an initial value of 0.97 mg. per hundred cubic centimeters of blood and another 1.02 mg.; both of these values are now considered normal values. Ingalls [21] reported a study of 15 children with scurvy with examinations of the blood and urine. The concentration in the blood of this group of patients was extremely low and varied from 0.0 to 0.16 mg. per hundred cubic centimeters. The ascorbic acid excreted

16. Wood, P.: A Case of Adult Scurvy, Lancet **2**:1405, 1935.

17. Schultzer, P.: On Saturation of Scorbutic Patients with Ascorbic Acid, Acta med. Scandinav. **88**:317, 1936.

18. Archer, H. E., and Graham, G.: Some Observations on Excretion of Ascorbic Acid, Lancet **1**:710, 1936.

19. Nisenson, A., and Cohen, A.: Adult Scurvy: Study of Urinary Output of Cevitamic Acid, Am. J. M. Sc. **194**:63, 1937.

20. Abt, A. F., and Epstein, I. M.: Cevitamic Acid (Ascorbic Acid) in the Treatment of Infantile Scurvy, J. A. M. A. **104**:634 (Feb. 23) 1935.

21. Ingalls, T. H.: Studies on the Urinary Excretion and Blood Concentration of Ascorbic Acid in Infantile Scurvy, J. Pediat. **10**:577, 1937.

in the urine was nil. This group of patients was not carried to saturation. Ingalls and Warren [22] also studied patients who were kept for a long time on a diet for the cure of peptic ulcer, whose condition they classified as asymptomatic scurvy, and reported that the values for ascorbic acid in the blood were in the same range as those in frank scurvy, namely, an average of 0.19 mg. per hundred cubic centimeters. These patients when given massive doses of vitamin C showed a rapid rise in the blood ascorbic acid. Taylor and co-workers [4b] reported determinations of blood ascorbic acid in clinical cases of scurvy as ranging from 0.11 to 0.55 mg. per hundred cubic centimeters. They also studied the response of their patients to 1 Gm. of ascorbic acid administered intravenously. A patient whose case they reported showed a rise in the blood ascorbic acid to 2.58 mg. per hundred cubic centimeters in thirty minutes; the concentration then fell in one and a half hours to 1.24 mg. This value was maintained for forty-eight hours. However, the initial value for the blood ascorbic acid of this patient was 0.61 mg., which indicates that he had been receiving antiscorbutic therapy prior to this experiment; nor is it stated whether he had been on a scorbutic diet during these twenty-four hours.

From these reports we gather that patients suffering from clinical scurvy have low concentrations of ascorbic acid in their blood and urine, but corresponding determinations may be just as low or indeed lower for some persons who show no signs of clinical scurvy. This seems paradoxic and makes one wonder whether the small amount of ascorbic acid in the body is in itself the factor responsible for the symptoms of scurvy. Indeed, there is a suggestion that in clinical scurvy there may be some anomaly in storage, as evidenced by the lower percentage excreted after prolonged feeding reported by Archer and Graham.[18]

CASE 1.—J. W. S., a man aged 28, was admitted to the medical ward of the hospital Jan. 7, 1937, complaining of pain in both thighs of one month's duration, black and blue areas on the right leg and thigh of ten days' duration and small red spots on both legs for two weeks. Limping because of the pain in the left leg was present for one week and weakness for several days. In the past five or six years there had been profuse bleeding from small cuts, and bleeding from the gums had been troublesome since 1928. In 1934 he noted pinpoint and pinhead sized purple spots over his legs and a loss of 12 pounds (5.4 Kg.) in weight. The dietary history revealed a complete abstention from citrus fruits and fresh vegetables. The patient stated that he had eaten no oranges or lemons for two years and no tomatoes, grapefruit or fresh vegetables in the last six years. His diet consisted almost exclusively of meat sandwiches, pie, doughnuts and coffee.

22. Ingalls, T. H., and Warren, H. A.: Asymptomatic Scurvy: Its Relation to Wound Healing and Its Incidence in Patients with Peptic Ulcer, New England J. Med. **217**:443, 1937.

The essential physical findings were as follows: All the teeth that were present were in an advanced state of caries, with many of the teeth buried below the gum surface and some projecting above the gum margin only a very short distance. The gums were not spongy and bled only slightly, but there were some areas of hyperemia. The mucous membranes of the pharynx and mouth were pale. The lower extremities revealed petechial hemorrhages, follicular in distribution, ecchymoses of the left thigh and lower part of the left leg and also of the right foot, and brawny induration of the muscles of the calves and right thigh. The left knee was swollen and tender, and the patient was unable to extend it completely. The left foot was held in equinovarus. The tourniquet test with a pressure of 80 mm. of mercury for three minutes was strongly positive.

The laboratory findings were moderate secondary anemia, a normal platelet count, a normal coagulation time and a normal bleeding time.

Roentgen examination of the chest, left hip joint and tibias showed no abnormality. The teeth showed absorption around the roots.

Case 2.—A. P., a man aged 69, entered the medical ward of the hospital June 10, 1937, complaining of bluish discoloration and pain in the calves present for six months and bleeding of gums and loosening of teeth, present for three years. Because of his poor financial circumstances his diet had consisted for the last twelve years of bread, pork, beans and coffee. In the last few years he had not eaten any fresh vegetables, oranges, lemons or limes or other fruits. He had been in fair health until three years before examination, when he began feeling weak and lost some weight. At that time his teeth began to loosen and his gums became swollen and began bleeding. Several teeth fell out. Six months before entering the hospital he noticed that the skin over the calves became blue and discolored and that the muscles became hard and very tender.

The physical findings included large ecchymoses of both the upper and the lower extremities and petechial hemorrhages of the legs. Characteristic induration and tenderness of the hamstring and quadriceps femoris muscles were also detected.

Patient J. W. S. (table 1) was on a ward diet with abundant vitamin C feedings for four days before the experiments were begun, and the basal excretion of ascorbic acid varied between 14.95 and 23.49 mg., with only two twenty-four hour periods in which it was 20 mg. or above. Patient A. P. (table 1) showed a much lower basal excretion, between 9.51 and 13 mg. Thus it may be seen that from the basal excretion alone the values for the first patient would fall almost within or just slightly below the normal limits. The second patient, while having low initial excretion, would still be thought to have values compatible with mild subclinical vitamin C deficiency. Hence our determinations of basal excretions of ascorbic acid were not diagnostic, as was pointed out also by Schultzer [17] and by Archer and Graham.[18] Why this should be so is difficult to explain except by the assumption that there are small amounts of other substances in the urine, such as thiosulfates and ergothioneine,[6] up to 6 mg., which may reduce the dye. In the lower ranges this interference may considerably distort the results, whereas in the higher ones the influence on the results would be inconspicuous. The

fact that the patients were on a vitamin-rich diet just before the experiment was begun may be of some importance.

After the administration of large doses of ascorbic acid was started, a striking difference was noted. Patient J. W. S. showed no sharp rise in excretion of the vitamin until 2,800 mg. had been given, and the highest excretion ever obtained was 271.2 mg., or 68 per cent of the

TABLE 1.—*Ascorbic Acid in Blood and in Urine of Patients with Scurvy*

	A. P.—Male			J. W. S.—Male	
		Mg. Ascorbic Acid			
Day	Diet	24 Hr. Collection of Urine	100 Cc. Blood Plasma	Diet	Mg. Ascorbic Acid in 24 Hr. Collection of Urine
1	Ward	9.51	0.3	Ward*	16.0
2		12.45	....		15.77
3		13.0	....		18.74
4	Vitamin C–free	Lost	....		20.0
5	diet plus 400	20.25	....		18.77
6	mg. C †	13.82	0.36		17.48
7		Lost	....		23.49
8		10.67	....		19.66
9		41.22	....	Vitamin C–free	27.2
10		40.72	....	diet plus 400	20.88
11		120.45	....	mg. C	28.6
12		45.29	....		31.5
13		24.68	....		24.7
14		26.45	....		29.1
15		151.05	....		37.7
16		175.5	....		130.9
17		242.09	....		205.8
18		268.08	0.59		214.83
19		193.93	....		191.6
20		215.04	....		245.7
21		187.65	....		229.2
22		258.75	....		252.12
23		223.44	....		226.8
24		245.78	0.92		259.2
25		273.0	....		261.9
26		265.2	....		271.2
27		221.56	0.63		
28		130.0	....		
29		220.83	...		
30		181.81	0.76		
31		133.2	....		
32		165.75	....		
33		242.4	0.94		
34		212.06	....		
35		291.09	....		

* Patient J. W. S. was on a ward diet with abundant vitamin C feedings before the experiments began; with day 1 of the experiment recorded here he was placed on the ward diet alone—a low vitamin diet.

† Doses of 400 mg. were given from day 4 to days 12, 13 and 14, when doses of 200, 0 and 200 mg., respectively, were given. On all subsequent days the doses were again 400 mg.

intake, although eighteen daily doses of 400 mg. were administered. In other words, saturation was not obtained although 7.2 Gm. of ascorbic acid was administered. The case of patient A. P. was even more striking in this respect. Although a sharp rise occurred on the eighth day of the administration of large doses of the vitamin and after 4,000 mg. had been given 268 mg. was excreted, the amount excreted then dropped from this value and a saturation value was not reached until a total of 12 Gm. had been taken. The excretion values oscillated sharply

and were below 200 mg. thirty days after the daily administration of 400 mg. was begun.

It will be seen that all the controls reached this point quickly, i. e., in seven days or less (table 2), and showed a rise in excretion of ascorbic acid on the first day. The exhausted subjects showed a rise in excretion of ascorbic acid on the third to sixth day and saturation several days later.

The studies of the blood plasma revealed even more interesting results. The control patients (table 2), although they were slightly undernourished with respect to vitamin C, showed a basal level of 0.52 mg. and 0.61 mg. per hundred cubic centimeters of plasma. The latter value may be considered on the lower border of normal.[4a] The blood plasma showed a sharp rise from these relatively low values soon after the high ascorbic acid dosage was started. One control (J. K.) showed 1.44 mg. of ascorbic acid per hundred cubic centimeters of blood plasma on the fifth day of high vitamin dosage, when the amount excreted in the urine was 144 mg. Another control (E. G.) showed 1.13 mg. of ascorbic acid per hundred cubic centimeters of blood plasma one day after the administration of the acid was started and when the amount excreted in the urine was only 78.85 mg. In other words, these controls and other nonscorbutic persons showed a rapid rise of ascorbic acid in the blood plasma to 1.1 mg. per hundred cubic centimeters or higher after one or several large doses of the acid (chart 1; table 2) and even before the urinary excretion reached a high level. The ascorbic acid in the blood, unlike that in the urine, reaches a certain level above which it does not go regardless of the amount of vitamin C given. Thus, in subject E. G. the plasma level was 1.13 mg. at 78.85 mg. urinary output, and at 370 mg. urinary output it was the same. In control J. K. the plasma value was 1.44 mg. at 144 mg. urinary excretion and only 1.21 mg. at 303 mg. excretion. With this method without the use of potassium cyanide (KCN) the value for ascorbic acid in the blood plasma during fasting was never above 1.54 mg. per hundred cubic centimeters.

Now contrast the behavior of the plasma ascorbic acid of the scorbutic patient (A. P.) with that of the plasma ascorbic acid of the controls. After twelve daily 400 mg. doses the blood plasma value was 0.59 mg. per hundred cubic centimeters, and this when the urinary value was 268 mg. The scorbutic patient can apparently excrete large quantities in the urine while the concentration in the plasma remains low. While the plasma value rose to 0.92 mg. per hundred cubic centimeters on the eighteenth day, it fell to 0.63 mg. after twenty-two consecutive days of high vitamin feeding. Such behavior, which may indicate a low renal threshold, has not been observed by us in any other condition and may

TABLE 2.—*Summary of Urinary Excretion and Blood Concentration of Ascorbic Acid for Various Subjects* *

Subject	Sex†	Average Basal Excretion per 24 Hr.	First Excretion Peak		Highest Excretion Peak	Days of High Vitamin Feeding	Average Daily Excretion from Peak to End of Experiment	Ascorbic Acid per 100 cc. Blood Plasma		Comment
			Days‡	Height				Lowest	Highest	
Normal										
E. G.	M	16.4	1	78.85	356.3	7	232	0.61	1.13	Compensated hypertensive heart disease
J. H.	F	25.05	1	156.2	336.0	3	279	....	....	Neurosis
J. G.	F	25.22	1	108.13	334.66	8	273	....	....	Compensated rheumatic heart disease
J. K.	M	14.9	4	94.69	336.96	16	242	0.52	1.44	Slightly exhausted, compensated rheumatic heart disease
Exhausted										
C. J.	M	14.2	6	140.8	310.5	11	266	0.38	1.47	Peptic ulcer
W. Von B.	M	17.4	3	99.5	369.0	11	245	0.32	1.19	Peptic ulcer
Hyperthyroid										
J. K.	F	19.65	1	85.86	276.76	12	183	1.40 (KCN)	1.92	
B. D.	F	12.7	5	72.67	269.22	14	196	....	....	
F. W.	M	19.65	3	81.90	228.12	10	188	....	....	
E. H.	F	11.19	5	110.0	230.33	13	184	0.69 (KCN)	1.37	
L. L.	F	14.19	3	111.28	296.0	17	226	0.77 (KCN)	1.90	
J. B.	F	19.94	2	96.0	263.0	14	188	0.78 (KCN)	1.74	
J. G.	F	57.03	1	91.8	256.5	10	187	....	....	
Patients with Malignant Tumors										
A. C.	M	7.1	3	41.0	248.8	24	142	....	....	Carcinoma of lung with metastasis to spine
M. L.	M	7.88	5	70.07	259.4	17	182	0.66 (KCN)	1.70	Carcinoma of stomach
M. C.	F	10.04	3	40.32	207.72	9	135	....	....	Carcinoma of stomach
J. W.	M	11.53	..	None	18.76	11	...	....	....	Carcinoma of lung; patient died of melanosarcoma
A. M.	F	13.68	4	112.2	220.5	10	193	....	....	
Patients with Slow Growing Malignant Tumors										
A. K.	F	13.9	1	81.89	331.3	15	239	1.04 (KCN)	1.43	Metastatic carcinoma to spine 10 yr. after primary lesion of breast
Patients Suspected to Have Malignant Tumors										
G. K.	M	12.1	3	81.0	330.0	10	258	0.69 (KCN)	1.9	Proved later to be chronic cicatricial ulcer
B. S.	F	3.82	4	192.2	338.0	10	267	0.53 (KCN)	2.31	Symptoms and findings disappeared
E. F.	M	6.77	5	57.94	328.95	17	230	0.57 (KCN)	1.64	Symptoms and findings disappeared

* All values given in milligrams.
† F indicates female; M, male.
‡ Days of high vitamin dosage.

be an anomaly peculiar to the scorbutic organism; i. e., a person suffering from clinical scurvy not only may have a deficiency of the substance in the body but may also be unable to store it satisfactorily.

PURPURAS

Although it should be unnecessary to point out that not all hemorrhagic diseases are dependent on vitamin C deficiency, still there has been in the literature a good deal of reference to the favorable effect of ascorbic acid on nonscorbutic hemorrhagic conditions [22] with the implication that there may be a deficiency of ascorbic acid in some of these.[3f] Those who published these reports did not claim, however, that there

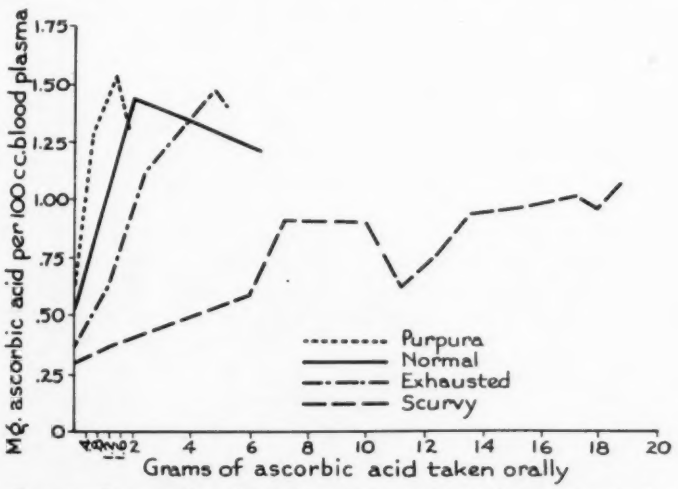

Chart 1.—Concentration of ascorbic acid in the blood plasma of scorbutic and nonscorbutic persons.

is a cause and effect relationship between the various purpuras and vitamin C. At times considerable diagnostic difficulty is encountered in ruling out scurvy in certain nonthrombopenic purpuras.

In fact, such was the case with our patient J. B. (table 3), who had a history suggestive of vitamin C malnutrition, some bleeding from the gums, a positive tourniquet test and profuse spontaneous subcutaneous and mucous membrane hemorrhages. Patient E. N. also gave a history of restriction of fresh fruits and vegetables due to various gastro-

23. Cotti, L., and Larizza, P.: Ueber den Einfluss der Ascorbinsäure auf die Blutgerinnung: Untersuchungen über den Wirkungsmechanismus "in vivo" der Ascorbinsäure in normalen und pathologischen Verhältnissen, Klin. Wchnschr. **15**:227, 1936. Glanzmann, E.: Zur Problem der Purpura fulminans, Schweiz. med. Wchnschr. **67**:829, 1937.

intestinal disturbances. She also had bleeding from the gums, subcutaneous ecchymosis and a mildly positive tourniquet test. Both of these patients had normal platelet counts and normal bleeding and coagulation times. A diagnosis of scurvy was strongly entertained until the studies of ascorbic acid were completed (table 3). These studies showed completely normal behavior. The immediate rise of ascorbic acid in the blood even while the amount excreted in the urine was low is especially striking when compared with the behavior of this vitamin in the scorbutic patient.

E. M. is a patient with true thrombopenic purpura who was studied for purposes of comparison. His response was completely normal.

TABLE 3.—*Patients with Purpura*

	J. B.—Female				E. M.—Male			E. N.—Female		
		Mg. Ascorbic Acid				Mg. Ascorbic Acid			Mg. Ascorbic Acid	
Days	Diet	24 Hr. Collection of Urine	100 Cc. Blood KCN	Plasma No KCN	Diet	24 Hr. Collection of Urine	100 Cc. Blood Plasma	Diet	24 Hr. Collection of Urine	100 Cc. Blood Plasma
1	Ward	....	0.95	0.66	Ward	15.6	....	Ward	.....	0.96 KCN
2		27.1	....	....		8.47	....		21.78	1.03
3		23.9	0.99	0.63		10.16	....		17.71	....
4		22.82	....	....		12.74	....		15.68	....
5	Vitamin C-	31.24	1.6	1.28		15.9	1.19	Vitmain C-	16.10	....
6	free diet	162.44	....	....		5.26	KCN	free diet	55.55	1.99
7	+ 400 mg.	255.34	1.78	1.54		7.95	1.13	+ 400 mg.	227.50	....
8		336.0	1.73	1.30	Vitamin C-	118.4	....		378.75	....
9		336.0	....	....	free diet	115.9	....		260.3	2.09
10		....	....	....	+ 400 mg.	283.12	....		308.25	....
11		....	....	....		178.2	1.76		328.25	....
12		....	....	....	"	149.49	....		....	....
13		....	....	....	"	97.2	1.51		....	....
14		....	....	....	"	312.84	....		....	....
15		....	....	....	"	333.3	....		....	....
16		....	....	....	"	333.3	1.7		....	....

While 1 of these patients, J. B., showed a favorable response to the high doses of ascorbic acid, this response appeared to be merely coincidental, since the symptoms recurred later in spite of continuance of this medication.

HYPERTHYROIDISM

According to the work of Szent-Györgyi,[24] Tauber and co-workers,[25] and others, the most likely action of ascorbic acid is in the capacity of an enzyme for cellular oxidation. By virtue of its strong reducing power it aids in the process of oxygen exchange. It has also been shown [3d] that scorbutic tissues take up less oxygen in vitro than normal tissues. These theoretic considerations led us to investigate the role of ascorbic acid in hyperthyroidism. During this investigation we

24. Szent-Györgyi, A.: Function of Hexuronic Acid in the Respiration of the Cabbage Leaf, J. Biol. Chem. **90**:385, 1931.

25. Tauber, H.; Kleiner, J. S., and Mishkind, D.: Ascorbic Acid Oxidase, J. Biol. Chem. **110**:211, 1935.

became aware of the work of Mosonyi,[26] who found that guinea pigs rendered hyperthyroid by medication with thyroid and thyroxin showed less tissue storage of the vitamin than similarly fed normal animals. He concluded that this phenomenon may be due either to increased excretion or to increased utilization. He did not make any studies of excretion on these animals.

All our hyperthyroid patients excreted less than 300 mg. of ascorbic acid on the daily 400 mg. doses; i. e., their excretion was always below what we should have expected in a normal person. The blood plasma showed normal saturation. Although most of these patients were on a high caloric diet that included an abundance of fresh fruits and vegetables, only 2 patients, J. K. and J. G., showed normal storage, as judged by the response to the first large dose. One of these patients (J. K.), although having a high initial concentration of ascorbic acid in the blood, excreted less than an average of 20 mg. per day, which also is evidence of increased utilization.

Further evidence of increased utilization is the average of the daily twenty-four hour amounts excreted from the first peak to the end of the experiment (table 2). This was below 200 mg. in all patients with hyperthyroidism except L. L., while the normal persons and the exhausted patients all showed an average of around 250 mg. The longer such an experiment was continued, the greater this difference would become, since the normal persons would continue having values of 300 mg. or above and the hyperthyroid patients would continue to show the lower levels of excretion.

One of our patients with hyperthyroidism, J. B., was studied both before and after thyroidectomy. Chart 2 shows a comparison of the amounts of ascorbic acid excreted in the urine during these two periods. The difference is marked. In the post-thyroidectomy period, when her basal metabolic rate was around ± 0 per cent, most of the values for daily excretion of ascorbic acid were above 250 mg., and the highest was 330 mg., while before thyroidectomy all except a single day's excretion were below 250 mg. The average of the daily values after the initial rise was 198 mg. before thyroidectomy and 250 mg. after thyroidectomy, or an increase of over 20 per cent.

MALIGNANT TUMORS

Several different investigators showed some relation between experimental malignant tumors and vitamin C. Musulin and co-workers [27]

26. Mosonyi, J.: Einfluss des Schilddrüssenhormons auf den Vitamin C-Stoffwechsel, Ztschr. f. physiol. Chem. **237**:173, 1935.

27. Musulin, R. R.; Silverblatt, E.; King, C. G., and Wood, G. E.: Titration and Biological Assay of Vitamin C in Tumor Tissue, Am. J. Cancer **27**:707, 1936.

found that Philadelphia no. 1 sarcoma had increased reducing power, and this was proved to be due to vitamin C by animal feeding experiments. Watson [28] showed the same to be true of the Jensen and the Walker sarcoma and of spontaneous mammary carcinoma. Benign tumors were shown to have much lower reducing power.[27] Voegtlin and associates,[29] using several different methods of determination, came to essentially the same conclusion. Vogelaar and Erlichman [30] showed

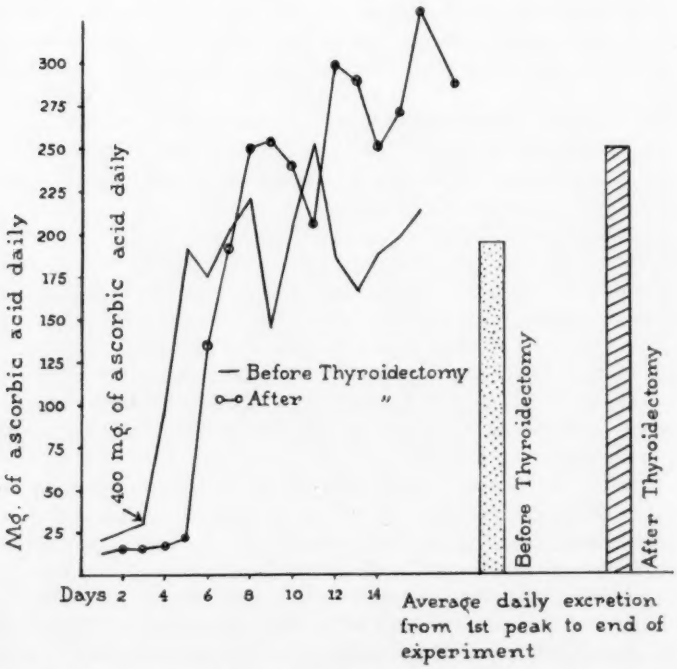

Chart 2.—Excretion of ascorbic acid in the urine of a patient with hyperthyroidism, (J. B., a woman aged 31) before and after thyroidectomy.

28. (a) Watson, A. F.: The Chemical Reducing Capacity and Vitamin C Content of Transplantable Tumors of Guinea Pigs and Rats, Brit. J. Exper. Path. **17**:124, 1936. (*b*) Watson, A. F., and Mitole, M.: A Note on the Reducing Activity of the Tissues of Normal and Tumor Bearing Rats and Mice, Biochem. J. **28**:811, 1934.

29. Voegtlin, C.; Kahler, H., and Johnson, J. M.: The Colorimetric and Spectrophotometric Determination of Vitamin C in Malignant Tumors, Am. J. Cancer **29**:477, 1937.

30. Vogelaar, J. P. M., and Erlichman, E.: Significance of Ascorbic Acid for the Growth in Vitro of Crocker Mouse Sarcoma 180, Am. J. Cancer **31**:283, 1937.

that ascorbic acid added to the artificial culture mediums in which the Crocker mouse sarcoma was grown stimulated cell division, inhibited cell degeneration and seemed to be necessary for the formation of intercellular fibers. Gordonoff and Ludwig,[31] however, found that "scorbutic mediums" produced almost as good cultures of malignant cells and fibroblasts as mediums containing vitamin C. Havas [32] showed that tumors of tomato plants treated with ascorbic acid attained twice as great a size as the nontreated tumors.

It seems logical to assume from physiologic considerations that rapidly growing malignant tumors use greater amounts of ascorbic acid by virtue of their rapid growth and hence more rapid oxidative processes. This was partly confirmed by the observation [28a] that tumor-bearing animals become more rapidly scorbutic than nontumor-bearing controls. We were interested in determining whether human beings suffering from various forms of malignant tumors would yield any confirmatory evidence for these theoretic considerations. Our subjects with malignant tumors included patients with gastric carcinoma, melanosarcoma and carcinoma of the lung with metastasis. All of these patients were selected as being completely afebrile, to avoid a confusing issue; none of them vomited or showed any evidence of increased utilization as judged by the amount excreted in the urine. None of these patients excreted over 300 mg. in twenty-four hours, and the average amount excreted daily from the first peak to the end of the experiment was between 135 and 193 mg. (table 2). J. W., a patient very ill with carcinoma of the lung, showed no increase in excretion of ascorbic acid after eleven daily 400 mg. doses. We felt that this was significant even though the patient was so ill that some loss of urine might have occurred.

We present also a group of 3 patients who were studied because the clinical and roentgen findings pointed strongly toward a diagnosis of malignant tumor. However, the studies of the urinary excretion showed a normal response (table 2). All of these patients are still alive, and the subsequent course of illness in each proves that the condition is nonmalignant. Patient G. K. continues having stationary roentgen findings, has gained weight since he was first studied in August 1937 and maintains his hemoglobin level and general health. The other 2 patients showed complete disappearance of the roentgenographic findings with clearing up of the clinical picture.

This observation may be of value as an aid in distinguishing a benign from a malignant lesion. The length of time of the urinary studies may be abbreviated in practice by giving the patient the 400 mg. doses of

31. Gordonoff, T., and Ludwig, F.: Ueber die Bedeutung der Vitamin für die Krebstherapie, Ztschr. f. Krebsforsch. **46**:73, 1937.

32. Havas, L.: Ascorbic Acid and Phytocarcinomata, Nature, London **136**:989, 1935.

ascorbic acid in addition to the usual diet for ten days or two weeks, until saturation has practically occurred. The patient can then be put on the scorbutic diet plus the pure ascorbic acid and the urine collected for one week or ten days; if in this length of time a normal excretion does not occur, the observation may be accepted as a sign of increased utilization, and hence a sign pointing to malignant growth.

A single patient with a malignant tumor (A. K.) among those whom we studied showed a response within normal limits to the high vitamin dosage. This patient had a mastectomy for carcinoma ten years previously. She had a recurrence of cutaneous lesions four years ago, which responded to roentgen treatment, and now, ten years after the removal of the primary tumor, she has what appears roentgenographically to be metastatic lesions of the thoracic spine, her general condition remaining good. This finding in no way refutes our original tenets, since this malignant tumor would appear from its duration to be very slow growing and relatively benign. A tumor of this type would be expected to have oxidative processes almost as slow as those of normal tissues and hence would be expected to use little ascorbic acid.

LEUKEMIA

Because of the rapid cellular proliferation in the hyperplastic bone marrow and the great acceleration in the production of leukocytes in this disease we thought there might be some increased utilization of ascorbic acid. We are not aware of any studies made of the concentration of ascorbic acid in the blood and urine in leukemia. A favorable therapeutic effect, however, was reported by Eufinger and Gaehtgens,[33] who claimed to have influenced the blood picture and clinical picture of their patient favorably by intravenous administration of crystalline ascorbic acid.

Our patient was afebrile, and his general condition was good. He was studied before and after total thyroidectomy to determine what influence the thyroid had on the utilization of ascorbic acid in leukemia. Chart 3 shows a comparison in this respect between a normal person and our patient with leukemia. Although their basal excretions of ascorbic acid were along the same level, in the leukemia patient before thyroidectomy no rise in excretion occurred until the eleventh day, and the amount excreted was never above 228 mg. per day, although the high vitamin feeding was continued for nearly thirty days. At the beginning of the experiment this patient's basal metabolic rate was + 11 per cent; later determinations were + 24 and + 35 per cent. Thyroidectomy was performed, and the basal metabolic rate decreased to only —2 per cent, although the patient had some signs of myxedema.

33. Eufinger, H., and Gaehtgens, G.: Ueber die Einwirkung des Vitamin C auf das pathologisch veränderte weisse Blutbild, Klin. Wchnschr. **15**:150, 1936.

The second curve showed an earlier rise in excretion, and on the twentieth day of the high vitamin feedings the amount was above 300 mg. However, there was a period of very low, almost basal excretion from the thirteenth to the eighteenth day. With these exceptions the curves are almost the same. It seems apparent that the thyroid had only slight influence on the increased utilization of ascorbic acid in this case, since the average daily amount excreted from the first peak to the end of the experiment was the same (chart 3).

The blood plasma concentration never reached so high a level as was observed in the normal persons or in the other patients with

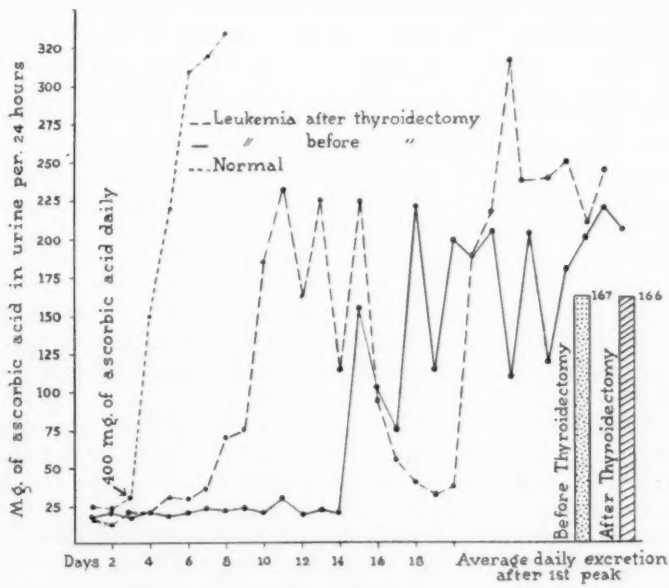

Chart 3.—Excretion of ascorbic acid in the urine of a normal person and in that of a patient with leukemia before and after thyroidectomy.

increased utilization. As regards the patients with hyperthyroidism and malignant tumors, although their urinary excretion of ascorbic acid was on the order of that of the leukemic patient, their blood concentration at saturation levels was 1.5 mg. per hundred cubic centimeters or above, whereas the leukemic patient did not show concentrations above 1.2 mg. before thyroidectomy, and after thyroidectomy the highest level was 1.29 mg. There was a further decrease from this value to 1.14 mg. at the time when the excretion of ascorbic acid was highest. These slightly lower values are probably of no significance.

PEPTIC ULCER

Numerous reports have appeared dealing with the state of vitamin C nutrition in patients on diets for the cure of peptic ulcer. Drigalski [3c] showed that with adherence to a strict ulcer diet for three weeks a decrease occurred in the ascorbic acid excreted. Archer and Graham [34] studied 9 patients with peptic ulcer who were on modified Sippy diets and found that their initial excretion of ascorbic acid varied from 8.5 to 26 mg. All of the values were lower than those for their 2 controls. They also showed a delayed rise in excretion of this substance on high vitamin feedings. They felt that this subclinical vitamin C deficiency was responsible for the poor healing found in some ulcerous patients after gastric surgical treatment. Ingalls and Warren [22] studied the blood ascorbic acid levels of 20 patients with peptic ulcer. All but 2 had very low levels, ranging from 0 to 0.6 mg. per hundred cubic centimeters. They called attention to the possible relation of vitamin C deficiency in these patients to wound healing and to hemorrhages. Rivers and Carlson [35] found correlations between capillary fragility and the concentrations of ascorbic acid in the blood and urine in their cases of bleeding peptic ulcer. In all but a single case there was decreased capillary fragility as demonstrated by the tourniquet test, and in all the cases the values for ascorbic acid in the blood and urine were subnormal. They feel that there is a possible causal relation between the increase in capillary fragility and the bleeding in this disease. They showed that the capillary resistance returned to normal after high vitamin C feedings.

Our patients on peptic ulcer diets showed evidence of vitamin C subnutrition as evidenced by urinary excretion of ascorbic acid in amounts below 20 mg. per twenty-four hours (table 2; chart 4), blood plasma concentrations of 0.3 to 0.4 mg. per hundred cubic centimeters, absence of response to 400 mg. doses of this vitamin till the third to sixth day and saturation after a week or ten days' feeding.

We were, however, primarily interested in the effect of alkaline medication on the absorption of ascorbic acid. Since this vitamin is highly unstable in alkaline solution in vitro, we thought that persistent medication with alkalis may interfere with absorption of the vitamin. On the basal milk and cream diet and 4 Gm. of alkalis every hour, patient W. P. (chart 4) excreted an average of 6.5 mg. of ascorbic acid per twenty-four hours for six days; after withdrawal of the alkalis he excreted 10.5 mg. per day for eight days. There was a prompt and persistent increase in excretion of the vitamin after the alkalis were

34. Archer, H. E., and Graham, G.: The Subscurvy State in Relation to Gastric and Duodenal Ulcer, Lancet **2**:364, 1936.

35. Rivers, A. B., and Carlson, L. A.: Vitamin C as Supplement in the Therapy of Peptic Ulcer: Preliminary Report, Proc. Staff Meet., Mayo Clin. **12**:383, 1937.

stopped, although the diet was practically vitamin C free. When we began giving the large doses of ascorbic acid (chart 4), the patient received no alkalis until he was "saturated" (excretion, 300 mg.). The addition of the alkaline powder caused a prompt drop in excretion of the vitamin, which persisted for six days and then rose to the previous level. If the alkaline medication or the neutralization of the hydrochloric acid in the stomach interfered with absorption of the vitamin, we should expect a continuance of the decreased excretion after the initial drop. Instead the excretion rose again in all cases to the previous high level. We interpreted this as meaning that the alkalis appeared to increase the amount of vitamin stored in the tissues—a sort of "super-

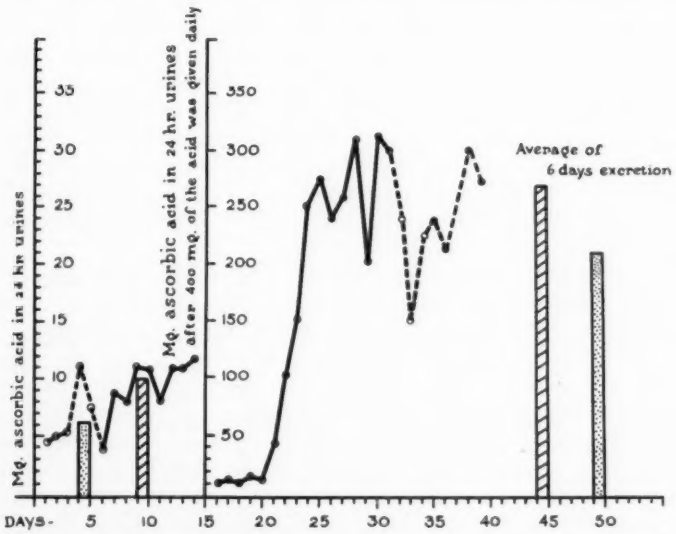

Chart 4.—Relation of the excretion of ascorbic acid to the medication with alkali in a patient with peptic ulcer.

At the right, under "Average of 6 days excretion," the cross-hatched column represents the excretion of ascorbic acid in a period when the subject (W. P.) received no alkalis; the stippled column, excretion in a period when the patient received 4 Gm. of alkali every hour.

saturation" of the tissues with the aid of alkalis—and when this state was reached the ascorbic acid was again excreted in the previous greater amounts. Therefore, instead of interfering with the absorption of the vitamin, the medication seemed to aid the body in retaining greater amounts of it. Hawley and co-workers [36] found that patients kept on a

36. Hawley, E. E.; Frazer, J.; Button, L., and Stephens, D. J.: Effect of Ingestion of Acid and Alkali upon Amount of Vitamin C in Urine, Proc. Soc. Exper. Biol. & Med. **34**:218, 1936.

constant diet showed greater excretion of ascorbic acid when acid salts were administered than when alkaline salts were given.

ASTHMA

It has been demonstrated by various workers [37] that the adrenal gland contains a larger concentration of ascorbic acid than any other organ in the body. Ordinarily the cortex of the gland has stronger reducing capacity than the medulla, but after anaphylactic shock, anger, ether or chloroform anesthesia or emotional reactions that entail an increase in the secretion of epinephrine, the reverse is found to be true.[38] These observations point to the possibility that ascorbic acid is connected intimately with the function of the adrenal gland, and probably it is active in the mechanism of the secretion of epinephrine.

A claim has also been made that vitamin C protects against sensitivity to arsphenamine,[39] but the lowering of the concentration of vitamin C in the blood has been considered by others [40] to be secondary to the reaction to arsphenamine. A claim has also been made that ascorbic acid may be a defense against anaphylactic shock, but this was denied by van Niekerk,[41] who showed that sensitized guinea pigs receiving large doses of vitamin C were unable to withstand anaphylactic shock any better than vitamin–C deficient controls.

Since epinephrine is so helpful in asthmatic attacks, we thought there might be some relation between this disease and ascorbic acid. Is the asthmatic patient unable to store the vitamin, with resultant malfunction of the adrenal gland because of the absence of this very important factor in the tissues? This question we set out to answer.

We studied 2 patients with clinical asthma of long duration who showed poor therapeutic response. One of these (S. P.) was malnourished and underweight because of severe restrictions on her diet due to her sensitivity to various foods. Her basal urinary excretion of ascorbic acid was low, 10 to 13 mg., and the concentration of the vitamin in the blood plasma was 0.46 mg. per hundred cubic centimeters. In spite of this we caused further depletion by putting her on a scorbutic diet for one week, both urine and blood showing a resultant drop in concentration of ascorbic acid. When she was given the 400 mg. of

37. Bourne, G.: The Role of Vitamin C in the Organism as Suggested by Its Cytology, Physiol. Rev. **16**:442, 1936.

38. Bourne, G.: Vitamin C, M. J. Australia **1**:339, 1934; footnote 37.

39. Cormia, F. E.: Experimental Arsphenamin Dermatitis: The Influence of Vitamin C in the Production of Arsphenamin Sensitiveness, Canad. M. A. J. **36**: 392, 1937.

40. Friend, D. G., and Marquis, H. U.: Arsphenamin Sensitivity and Vitamin C, Am. J. Syph., Gonor. & Ven. Dis. **22**:239, 1938.

41. van Niekerk, J.: Anaphylaxis and Vitamin C, J. Allergy **8**:446, 1937.

ascorbic acid daily, there was some slight increase immediately, but a peak did not occur until the fifth day; in other words, about 1,800 mg. of vitamin was stored. Saturation occurred after a few more days, with excretion of over 300 mg. daily. Her fasting blood plasma concentration did not rise above 1.38 mg. per hundred cubic centimeters, which is slightly lower than the value for our controls. We thought this might conceivably have some effect on the syndrome, so we decided to give the patient some crystalline ascorbic acid intravenously. During one severe attack, occurring after the patient was saturated, we gave her 1,000 mg. intravenously, but it had no effect on the attack, and epinephrine had to be administered.

The other patient showed evidence of good vitamin C nutrition both as to the concentration in the blood plasma and the amounts excreted in the urine and as to quick saturation, but his asthmatic attacks continued unabated. Since the concentration in the blood did not quite reach the optimal saturation level, we thought that this might be related to the

TABLE 4.—*Cevitamic Concentration of Ascorbic Acid in Blood Plasma and in Ascitic Fluid*

	Blood Plasma		Ascitic Fluid	
Patient	Amount of Dye, Cc.	Mg. Ascorbic Acid per 100 Cc.	Amount of Dye, Cc.	Mg. Ascorbic Acid per 100 Cc.
C. A.	0.47	1.48	0.46	1.45
C. A.	0.40	1.23	0.39	1.2
M. D.	0.20	0.61	0.20	0.61
J. N.	0.20	0.61	0.19	0.59

repeated injections of epinephrine which these patients received. We were unable to demonstrate a depressing effect on the ascorbic acid in the blood by giving epinephrine hypodermically to another patient.

PORTAL CIRRHOSIS

Because of its size the liver is the largest storehouse for vitamin C in the body. The question arises whether in clinical conditions accompanied by widespread destruction of liver parenchyma there may not be inadequate storage of this vitamin. A patient with portal cirrhosis who had unquestionable hepatic damage was chosen. This patient had ascites, moderate jaundice, a reversal of the albumin-globulin ratio, and a small liver.

He was put on a vitamin C–free diet for eight days. Although the urinary excretion of the vitamin was close to 20 mg. per twenty-four hours, the blood concentration was only 0.36 and 0.39 mg. per hundred cubic centimeters. The high initial amount excreted is interpreted as due to interference of the bilirubinuria with the titration at these lower figures.

When the administration of the 400 mg. doses of ascorbic acid began, no sharp rise in excretion occurred until the sixth day, during which time over 2,000 mg. of the vitamin was retained. This is a usual finding in an exhausted patient, and proved that in spite of the destruction of liver parenchyma, storage of the vitamin was still possible. The excretion of the vitamin continued rising until a level compatible with normal was reached. At one time 290 mg. and at another time 297 mg. was excreted; lower levels were observed at other times. There are two reasons why a higher excretion was not maintained throughout. This patient had a low elevation of temperature every afternoon. Moreover, loss of ascitic fluid was a source of loss of ascorbic acid.

An additional interesting observation made by us in this case is that ascitic fluid, at least in portal cirrhosis, contains the same concentration of ascorbic acid as does blood plasma (table 4). We used the same method in both determinations. The storage of the vitamin in the ascitic fluid results in recovery of smaller amounts in the urine.

CONCLUSIONS

1. Persons normal from a dietary point of view show a prompt rise in urinary excretion and blood concentration of ascorbic acid, with rapid "saturation," when large doses are administered by mouth.

2. "Exhausted" patients show a delay in saturation, but their blood concentration rises above 1 mg. per hundred cubic centimeters before a great rise in the urinary excretion occurs.

3. The diagnostic features of scurvy seem to be: a lowered renal threshold for ascorbic acid, extreme depletion of the body stores and an unusual delay of saturation as evidenced by urinary excretion.

4. There seems to be increased utilization of ascorbic acid in diseases accompanied by increase in oxidative processes or in cellular proliferation, i. e., in (*a*) malignant tumor, (*b*) hyperthyroidism and (*c*) leukemia. This observation may be of interest from both a diagnostic and a therapeutic point of view.

5. Alkali medication does not interfere with absorption of ascorbic acid in cases of peptic ulcer. Treatment by "Sippy" diets when prolonged leads to depletion of stores of ascorbic acid.

6. Patients with clinical asthma show no abnormality of storage. Large doses of ascorbic acid given intravenously or by mouth have no ameliorating effect on the attacks.

7. The damage of the liver in portal cirrhosis does not interfere with storage of ascorbic acid. Ascitic fluid contains the same concentration of ascorbic acid as blood plasma.

INCIDENCE OF PULMONARY AND EXTRA-PULMONARY TUBERCULOSIS IN ANTHRACITE COAL MINERS

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Pulmonary tuberculosis is a frequent complication of anthracosilicosis. A study made by the United States Public Health Service [1] in the anthracite region of Pennsylvania in 1934 showed that 20.4 per cent of miners and mine laborers over the age of 55 (i. e., those having the longest exposure to mine dusts) had clinical tuberculosis. A survey has just been completed at the White Haven Sanatorium [2] of the incidence of tuberculosis among anthracite miners coming to autopsy in the various institutions in Luzerne County. Of 541 cases in which autopsy was performed on miners, pulmonary tuberculosis was the principal cause of death in 21.3 per cent, whereas of 730 cases in which autopsy was performed on male nonminers of the same age during the same period in the same institutions tuberculosis was the cause of death in 8.9 per cent. In other words, pulmonary tuberculosis is more than twice as common in miners as in nonminers. In view of the frequency of pulmonary tuberculosis complicating anthracosilicosis, a study of the frequency with which extrapulmonary tuberculosis may occur in patients with the combined diseases should be of value.

Between May 1934 and May 1938 a complete postmortem examination was made at the White Haven Sanatorium of 50 patients with anthracosilicosis associated with pulmonary tuberculosis and of 84 patients with nonanthracosilicotic pulmonary tuberculosis. During approximately the same period laryngologic examinations were made by Dr. Joseph Donnelly [3] of 100 tuberculous miners and 265 tuberculous adult male nonminers. The data obtained form the basis for this study.

Of the 50 patients with anthracosilicosis 20 per cent had intestinal tuberculosis, while of the 84 with pulmonary tuberculosis not associated with anthracosilicosis, 51 per cent had intestinal tuberculosis.

From the White Haven Sanatorium.

Read at a meeting of the Laënnec Society, Philadelphia, April 26, 1938.

1. Special Bulletin 41, Commonwealth of Pennsylvania, Department of Labor and Industry, 1934.

2. Charr, R.; Cohen, A. C., and Bettag, O. L.: Internat. Clin., to be published.

3. Donnelly, J.: Personal communication to the author.

Age.—Six patients with anthracosilicosis were below 30 years of age; of these, 4 (67 per cent) had intestinal tuberculosis. Fifty nonminers were below the age of 30; of these 29 (58 per cent) had intestinal tuberculosis. Of 44 tuberculous miners above the age of 30, 6 (14 per cent) had intestinal tuberculosis; of the 34 tuberculous nonminers, 14 (41 per cent) had intestinal tuberculosis.

Extent of Anthracosilicosis.—Thirty-five per cent of the 20 patients with early or moderately advanced anthracosilicosis had intestinal tuberculosis, whereas only 10 per cent of the 30 patients with far advanced anthracosilicosis had involvement of the intestines (table 1).

Type of Pulmonary Tuberculosis Complicating Anthracosilicosis.—Eleven (55 per cent) of the 20 patients with early or moderately advanced conditions had acute caseous lesions, and 9 (45 per cent) had fibrotic lesions. Of those having caseous lesions, 5 (45 per cent) showed intestinal tuberculosis; and of those having fibrotic lesions, 3

TABLE 1.—*Frequency of Intestinal Tuberculosis According to Degree of Anthracosilicosis*

	Anthracosilicosis		
	Absent	Minimal or Moderately Advanced	Far Advanced
Number of patients	84	20	30
Number with intestinal tuberculosis	43	7	3
Percentage with intestinal tuberculosis	51	35	10

(33 per cent) had intestinal involvement. Of 30 patients with far advanced anthracosilicosis, 3 (10 per cent) had acute caseous lesions, while 27 (90 per cent) had fibrotic tuberculosis. One patient (33 per cent) in the group with caseous lesions and 1 (4 per cent) in the group with fibrotic lesions showed intestinal involvement. In only 3 of these patients was the pulmonary tuberculosis minimal; in all the rest it was far advanced, with cavitation.

Laryngeal Tuberculosis.—During approximately the same period a study was made of 365 larynges, 100 of the subjects being miners and 265 being male nonminers. All examinations were made by the same laryngologist. Of the miners, 27 per cent had laryngeal tuberculosis; of the nonminers, 31 per cent had laryngeal tuberculosis. This difference becomes significant when it is considered that in the miners the condition was much more severe; 57 per cent of the miners and only 12 per cent of the nonminers died of tuberculosis in the sanatorium. Of the miners who died of tuberculosis, 33 per cent had laryngeal tuberculosis; whereas of the nonminers who died of tuberculosis, 59 per cent had laryngeal tuberculosis. Because the incidence of laryngeal tuberculosis is said to be different in different age groups, the age group in

which most of the miners were observed (30 to 49 years) was compared with the same age group for nonminers. Of the 33 miners who died of tuberculosis between the ages of 30 and 49 years, 33 per cent had tuberculous laryngitis; while of the 15 nonminers of the same age who died of tuberculosis, 47 per cent had tuberculous laryngitis.

Tuberculosis of Other Organs.—Examination of the records of the necropsies previously mentioned for patients with extrapulmonary tuberculosis involving organs other than the larynx or the intestines did not provide enough cases of tuberculosis of any one organ to make comparisons between miners and nonminers significant. However, 32 per cent of 50 miners had such lesions, as against 46 per cent of 37 adult male nonminers (table 2).

TABLE 2.—*Frequency of Extrapulmonary Tuberculosis in Men Dying of Far Advanced Pulmonary Tuberculosis*

	Intestines			Larynx			Other Extrapulmonary Organs		
Anthracosilicosis	No. of Patients	No. with Tuberculosis	Percentage with Tuberculosis	No. of Patients	No. with Tuberculosis	Percentage with Tuberculosis	No. of Patients	No. with Tuberculosis	Percentage with Tuberculosis
Present	30	10	20	54	18	33	50	16	32
Absent	37	19	51	32	19	59	37	17	46

COMMENT

The prevalence of intestinal tuberculosis in association with ordinary pulmonary tuberculosis is well known; various investigators have observed it at necropsy in from 50 to 90 per cent of cases in which death was caused by tuberculosis.[4] Its relative infrequency as a complication of tuberculous anthracosilicosis is striking.

It has been recognized that intestinal tuberculosis is commoner in young than in old tuberculous patients. This is also true of anthracosilicosis associated with pulmonary tuberculosis; of miners above the age of 30, only 14 per cent had intestinal tuberculosis; whereas of the younger group, 67 per cent showed it. The reason appears to be that among the younger miners the degree of anthracosilicosis was less and the pulmonary tuberculosis was more acute, resembling tuberculosis in nonminers. However, age per se does not appear to be the determining factor in the incidence of intestinal tuberculosis in miners; most of the miners with far advanced anthracosilicosis were 30 years of age and older; and in this age group the miners showed a 14 per cent

4. Rubin, E. H.: Am. Rev. Tuberc. **22**:184, 1930. Fishberg, M.: Pulmonary Tuberculosis, ed. 4, Philadelphia, Lea & Febiger, 1932, vol. 2, p. 153.

incidence of intestinal tuberculosis, while the nonminers showed an incidence of 41 per cent.

In combination with early or moderately advanced anthracosilicosis, intestinal tuberculosis occurred with nearly the same frequency as in combination with nonanthracosilicotic pulmonary tuberculosis. In association with these conditions pulmonary tuberculosis showed a definite tendency toward rapid spread and destruction. The amount of intestinal involvement, when this occurred, was great; often the entire length of the ileum and cecum and other parts of the large bowel were involved. In the presence of far advanced anthracosilicosis, tuberculosis of the intestines occurred rarely; when it did occur the lesions were, as a rule, few and not extensive (table 1).

It seems that anthracosilicosis favors the development of pulmonary tuberculosis. Sokoloff [5] found that the incidence of pulmonary tuberculosis increased in direct proportion to that of anthracosilicosis, and the previously mentioned report of the United States Public Health Service [1] emphasized the fact that the incidence of pulmonary tuberculosis is greatest among miners who have been longest exposed to mine dusts. The incidence of intestinal tuberculosis, on the contrary, is least among those who have the highest degree of anthracosilicosis.

The rarity of intestinal tuberculosis in the late stage of anthracosilicosis is probably due to the presence of pulmonary fibrosis and the customary chronicity of pulmonary tuberculosis in these patients, as observed by Landis.[6] When a cavity forms in the center of an anthracosilicotic mass it enlarges very slowly. Often such a cavity contains mucoid material having only a few tubercle bacilli or none; the wall of the cavity and the surrounding tissue when examined microscopically show few tubercle bacilli or none. Furthermore, the blood vessels in the anthracosilicotic mass and particularly in the neighborhood of the cavity always undergo extreme sclerosis, frequently followed by thrombosis. Blood vessels completely obliterated by fibrosis are frequently observed.[7] Such vascular changes tend to prevent the spread of tubercle bacilli.

The pathogenesis of secondary tuberculosis of the intestines is not clearly understood. The condition may be due to direct infection from swallowed sputum containing tubercle bacilli or to a spread through the lymphatic system or the blood stream. Animal experiments have not given convincing results.[8] It is easier to produce tuberculous enteritis in healthy animals by parenteral injection than by feeding tuberculous

5. Sokoloff, M. J.: Am. Rev. Tuberc. **34**:700, 1936.
6. Landis, H. R. M.: J. Indust. Hyg. **1**:117, 1919.
7. Charr, R., and Riddle, R.: Am. J. M. Sc. **194**:502, 1937.
8. Maxwell, J.: Tubercle **17**:337, 1936.

material, but the experimental work is not conclusive. In this study all patients with intestinal tuberculosis associated with either anthracosilicosis or pulmonary tuberculosis had sputum which repeatedly yielded bacteria and showed a high Gaffky grading; on the other hand, there were many patients with such sputum who had no intestinal lesions. Three of the 8 patients suffering from anthracosilicosis with intestinal involvement had tubercles in the kidneys as well; in these cases the mode of infection may have been through the circulatory system.

As to the symptoms of intestinal tuberculosis, it was interesting to note that in 5 cases of anthracosilicosis with tuberculosis of the intestines there was no complaint suggesting intestinal involvement. In 5 cases abdominal pain, tenderness in the right lower abdominal quadrant, diarrhea, nausea and vomiting were present from time to time either singly or together. Walsh [9] and also Boles and Gershon-Cohen [10] have observed that clinical symptoms and signs—abdominal pain, tenderness, diarrhea and rigidity—are of little value as diagnostic criteria. This has been substantiated in the present study. Repeatedly, symptoms characteristic of acute appendicitis were observed, but actually acute appendicitis is not commonly associated with pulmonary tuberculosis. Tuberculosis of the appendix is not uncommon, however; of the 53 patients with intestinal tuberculosis studied, 9 (17 per cent) had macroscopic ulcers of the appendix. The danger of perforation of the intestine is small, this complication having occurred in only 1 patient (2 per cent) of this series.

Patients with far advanced anthracosilicosis, with or without tuberculosis, frequently complain of anorexia, vague abdominal discomfort, flatulence and diarrhea alternating with constipation. These symptoms are perhaps due to chronic passive congestion of the gastrointestinal tract secondary to myocardial weakness, which is a common occurrence in cases of anthracosilicosis.

SUMMARY AND CONCLUSIONS

Pulmonary tuberculosis is more frequent in anthracite miners than in nonminers of the same age and sex.

Tuberculosis of the intestines, the larynx and other extrapulmonary organs is, however, less frequent in miners than in nonminers.

In the majority of cases of intestinal tuberculosis associated with anthracosilicosis there were no symptoms referable to the gastrointes-

9. Walsh, J.: New York M. J. **90**:100, 1909.

10. Boles, R. S., and Gershon-Cohen, J.: Intestinal Tuberculosis: Pathologic and Roentgenologic Observations, J. A. M. A. **103**:1841 (Dec. 15) 1934.

tinal tract. Pain, tenderness and diarrhea, though sometimes present, could not be depended on as diagnostic criteria.

The relative infrequency of extrapulmonary tuberculosis in the presence of anthracosilicosis is due to the extensive fibrosis and relative avascularity of the lungs and the chronicity of the pulmonary tuberculosis usually present in these patients. These factors apparently tend to prevent the spread of tuberculous infection to other parts of the body.

Dr. Joseph Walsh gave permission for the use of the material presented in this study.

RELATION OF HEREDITARY PATTERN TO CLINICAL SEVERITY AS ILLUSTRATED BY PERONEAL ATROPHY

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CHARLOTTE, N. C.

Field work in the inheritance of human disease has brought to light two striking phenomena:

First, in regard to many of the diseases due to unit traits, that is, conditioned by a single defective gene, a wide survey of 50 to 100 families possessing such a trait usually shows a triple pattern of inheritance: dominant, sex-linked recessive and simple recessive.

How general this rule is in human, animal or plant genetics is not known, nor is it obvious why the same trait should be dominant in 1 family and recessive in a second and in a third ride the sex chromosomes down the generations, becoming manifest only in the males.

The second phenomenon, a corollary of the first, is that the pattern of inheritance determines the age of onset and the clinical severity of various morbid unitary traits, as may be seen by a study of peroneal atrophy (Charcot-Marie-Tooth type).

Lenz [1] repeatedly called attention to the mildness of dominant traits and by way of explanation said: "In the case of dominant heredity, severe and rapidly progressing forms would not be able to maintain themselves in existence." This idea of the survival of the fittest only might well be true for muscular dystrophy should the children not survive to the reproductive age, but the same explanation cannot hold for many other unitary traits which are nonlethal even when severe, such as retinitis pigmentosa and peroneal atrophy. A much more rational explanation seems to be that the behavior of the genes determines the age of onset and the clinical severity of the disease.

Last year I showed [2] that when retinitis pigmentosa is dominant, those affected are only half blind, night blind or "moon-eyed," the age of onset being between 25 and 40 years, and the severity rarely pro-

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1. Baur, E.; Fischer, E., and Lenz, F.: Human Heredity, New York, The Macmillan Company, 1931, chap. 9, pp. 407 and 410.

2. Allan, W.: Eugenic Significance of Retinitis Pigmentosa, Arch. Ophth. **18**:938 (Dec.) 1937.

gressing to total blindness even after the age of 60 years; when the condition is sex-linked recessive, the age of onset is in the second or third decade, and complete blindness supervenes between the ages of 40 and 50; when it is simple recessive, sight begins to fail in the first decade, and in such cases children become stone blind before they are 20.

The same rule, or law, holds in regard to peroneal atrophy. The afflicted members of the family in which peroneal atrophy is dominant (fig. 1) notice beginning disability about the age of 30 but are able to plough their fields and pick cotton past the age of 70. The atrophy is moderate, or there may be only pes cavus.

When peroneal atrophy is sex-linked recessive (fig. 2), the boys notice atrophy about the middle of the second decade and by the time they are 25 are too disabled for such occupations as watchmaking and bookkeeping, are on crutches or are bedridden.

When it is a simple recessive trait (fig. 3), peroneal atrophy begins before the age of 8 years, and in the second decade its victims become hopeless cripples.

The explanation seems to be this: Those in whom the trait is dominant, who are all heterozygous in case of these uncommon diseases, receive one defective gene from the affected parent and one normal gene from the unaffected parent; such a pair of genes, half good and half bad, causes half blindness or half crippling with late onset.

The boys with a sex-linked recessive trait, of course, receive one defective gene from their mother, without any corresponding normal gene on the chromosome they receive from their father, and the trait is correspondingly more severe, with an earlier onset.

When the trait is simple recessive, each parent supplying a defective gene, there is nothing to ameliorate the intensity of the disease, and it is very severe, with an early onset. This behavior of the genes explains the relation of hereditary pattern to clinical severity and age of onset.

These fundamental laws of the genetics of human pathology have some highly practical bearings on voluntary negative eugenics. When dominant, these diseases may not be severe enough to impel the afflicted parents to forswear propagation. However, when sex-linked recessive or simple recessive, the traits are disastrous enough to make voluntary birth control a welcome discipline in these families whenever the parents are properly informed. The simplicity with which a program for negative eugenics can be instituted and carried out has been repeatedly emphasized [3] and need not be gone into here. Suffice it to say that

3. Allan, W.: The Relationship of Eugenics to Public Health, Eugenical News **21**:73 (July) 1936; Medicine's Need of Eugenics, South. Med. & Surg. **98**:416 (Aug.) 1936.

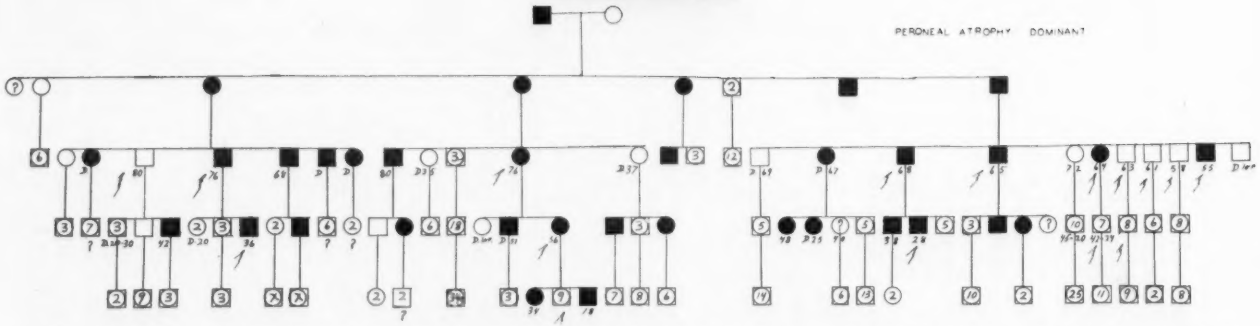


Fig. 1.—Pedigree 1 and G III 26. In all pedigrees squares denote men; circles, women; circles within squares, both sexes; black, peroneal atrophy; white, normal; figures within symbols, number of persons; figures below symbols, age of person or of oldest of group. The arabic figures following the designation of the generation indicate the place of each symbol in its generation, counting from left to right. Fingers point to those whom I examined. Circles or squares containing smaller circles or squares within them in pedigrees 2 and 3 denote carriers of the trait.

many of the diseases that wreck childhood will be voluntarily suppressed or eliminated whenever, after a study of the hereditary pattern in the individual family, those concerned are warned as to what is in store for their children.

PEDIGREE 1

This pedigree (fig. 1), which shows peroneal atrophy as a dominant unit trait, was started with G III 26, whose photograph accompanies the chart. He began to notice trouble with his ankles at the age of 25 years; at 55 he had marked atrophy of the muscles below the knees and elbows but got around well.

It was known by many of his generation that the grandfather, G I 1, had badly crippled feet. G II 1 married early and moved to Missouri, and nothing more is known of her. G II 2 and her 6 children had no crippling. G II 3 married her second cousin (on the mother's side of the family), who was not reported as crippled; however, she and 5 of her 7 children had peroneal atrophy. Her oldest daughter, G III 2, married and moved to another county early in life, but the relatives stated that the family had no atrophy. The other 2 girls in this sibship, G III 3 and 8, both manifested atrophy after typhoid in the early twenties, but the condition of their children is not known. I found G III 4 shucking corn at the age of 80 and failed to detect atrophy or foot drop; one of his sons was said to walk on the outside of his feet and to be unable to plow, but as this man was away at a corn husking I failed to see him. Apparently the trait skipped a generation here. Whether the high proportion of affected children in this sibship was a matter of chance or was due to the kinship of the parents is uncertain. The next 2 sons, G III 5 and 6, both had foot drop with some atrophy of the hands, and each had an affected son. I found G III 5 mending harness; he had mild atrophy of the hands and foot drop. The affected son G IV 8 was plowing. He had pes cavus and could not avert his feet. The last son, G III 7, was severely crippled, but I could get no report on his 6 children. The fourth child, G II 4, and 2 of her 7 children, G III 9 and 12, had atrophy. G III 9's daughter, G IV 14, had atrophy, but the condition of her 2 sons was not known. G III 12, when seen at the age of 76, had marked atrophy of both hands and feet; her son, G IV 18, had peroneal atrophy, but as his oldest child was only 28 at the time of investigation it was too early to know what will happen to his children.

G IV 19 had marked outward rotation of the right ankle, with peroneal atrophy coming on a few years before she was seen. Two (G V 11 and 13) of her 11 children were showing the early signs of peroneal atrophy.

G II 4 lost 2 daughters when they were about 35 years old; there was no atrophy in the 6 children of one (G III 10), but 2 (G IV 20 and 22) of the 5 children of the other (G III 13) had crippled feet. As G III 13 herself was reported not to have had atrophy, either the trait skipped a generation, or she died before it became manifest.

The next daughter, G II 5, and 1 of her 4 children are reported to have had the family disability.

The next 2 sons, G II 6, and the 6 children of each were free from atrophy. The third son, G II 7, was severely crippled and died childless in old age. The last son, G II 8, was moderately crippled. His oldest son, G III 17, and this son's 5 children were all free from atrophy. The second child, G III 18, and 2 of her 8 children, G IV 24 and 25, had atrophy, while the status of a third child, G IV 26, was doubtful.

I examined G III 19 and 1 of his affected sons, G IV 29, neither of whom was badly disabled. The other son, G IV 28, was a guard at a convict camp, which indicates that his atrophy was not severe. All 3 noticed beginning lameness at about the age of 25.

I examined G III 20 when he was 65 years old and found him cutting wood with difficulty. He first noticed beginning lameness at 20. His affected son, G IV 32, had atrophy of the hands, while the affected daughter, G IV 33, had involvement of both hands and feet. The condition of one daughter, G IV 34, was uncertain, since she married early, moved away and had not kept in touch with her family. None of the grandchildren of G III 18, 19 and 20 was old enough to show the trait.

The fifth child, G III 21, and her 10 children escaped the family affliction. I saw that the sixth child, G III 22, had typical atrophy of both hands and feet, but none of her 7 children, ranging in age from 42 to 24 years, had as yet manifested atrophy. Neither G III 23 nor any of his 8 children had peroneal atrophy, but 3 of these children inherited lobster claw hands from their mother's family.

The eighth child, G III 24, and his 6 children as well as the ninth child, G III 25, and his 8 children were all free from atrophy. The tenth child, G III 26, who has already been described, had no children. G III 27 died in infancy.

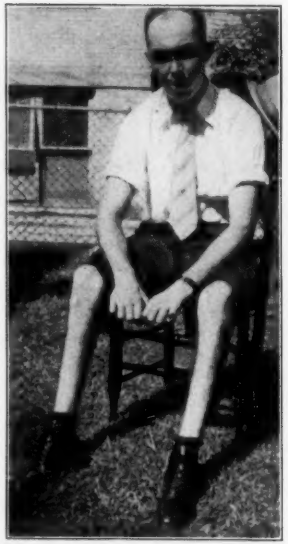
Peroneal atrophy in this family begins any time between the ages of 25 and 50 and varies from a light to a moderately severe handicap in the life of these farmers and their wives. In some cases only the feet are involved; in others, the arms and hands later become atrophied. Although occupations that require much walking, such as plowing and cooking, may be interfered with, none of the family has ever quit working at the occupations which require less locomotion.

Since peroneal atrophy is inherited here as a simple dominant trait, coming on late and never causing total disability, the affected members of this family look on it as a handicap rather than a disaster and probably would not give up having children, even if warned that half their children will be similarly affected.

PEDIGREE 2

In 1936 the young man G IV 43, aged 25 years, whose photograph accompanies this pedigree (fig. 2), was referred to me because his hands were too severely disabled to carry on his business of watchmaking. He wore braces below the knees. The disability was typical hereditary peroneal atrophy. With this man's help I combed Cabarrus County, working out the family history and visiting the relatives. His great-grandmother, G I 4, brought the trait into the family, since 2 of her brothers, G I 5 and 9, had it. Another brother, G I 8, married a wife, probably a kinswoman, who as part of her dower also brought along peroneal atrophy, passing it down in the collateral branches G III 29 and 30 and G IV 56 and 58. Although I have visited the 4 living members of the second generation, aged 77 to 92, this wife's name has been lost. A glance at the chart shows the pattern here to be sex-linked recessive, with 1 instance in a woman, G III 30, of incomplete recessiveness.

The great-grandmother's oldest son, G II 1, was severely crippled, and his two daughters, G III 1 and 4, were of course transmitters. I visited the older



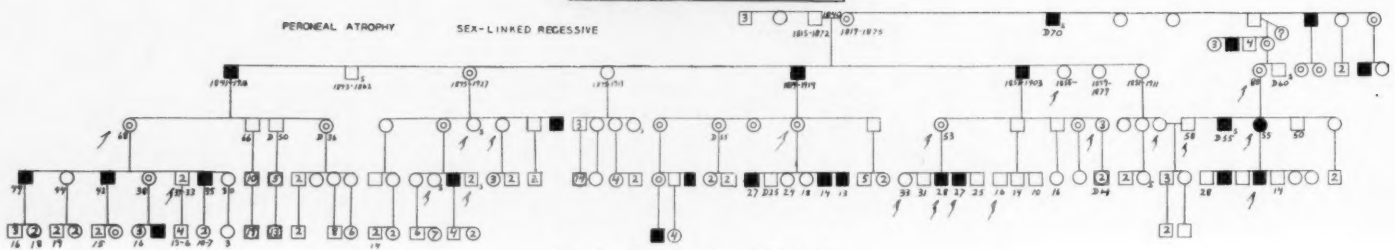


Fig. 2.—Pedigree 2 and G IV 43.

of these daughters, aged 68, who reported that 3 of her 5 sons, G IV 1, 3 and 6, were badly crippled; of her 3 daughters (G IV 2, 4 and 7), 1 (G IV 2) had 2 sons, G V 3, who escaped; 1 (G IV 4) passed the trait to her only son, G V 8, and 1 (G IV 7) had no sons. The other daughter of G II 1 died at 36, leaving 2 normal boys, G IV 10 and 3 girls, of whom 1 (G IV 11) was single, 1 G IV 12) had 8 normal boys and 1 (G IV 13) had only girls.

G I 4's second child, a son killed in the Civil War, presumably was normal. Her third child (G II 3) was a carrier, passing the trait to 1 (G III 10) of her 2 boys. Of G II 3's 4 daughters, 3 married; the oldest (G III 5) had 1 normal boy (G IV 14) and 1 daughter (G IV 15), whose sons were too young for one to know about their inheritance.

G III 6, the second daughter, was a carrier, 1 (G IV 18) of her 3 boys being affected; her only married daughter (G IV 16) had 6 boys, all normal when investigated.

G III 8 had 2 normal boys and was probably not a carrier.

G I 4's fourth child (G II 4) was probably normal, as her 3 boys (G III 11) were normal as well as the 2 sons (G IV 26) of her daughter.

G I 4's fifth child (G II 5) was only moderately crippled, but his 4 grandsons and his great-grandson showed the severity usually seen when this trait is inherited as a sex-linked recessive.

G II 5's oldest daughter (G III 15) had 2 sons, 1 of whom was crippled (G IV 29), and 1 daughter (G IV 27), who passed the trait to her only son (G V 23). The second daughter (G III 16) had 2 sons, who by chance escaped atrophy. The third daughter (G III 17) was single, and the fourth daughter (G III 18), whom I visited, passed crippling on to 3 (G IV 32, 36 and 37) of her 4 boys.

G II 6 was severely crippled: the elder of his 2 boys (G III 21) was reported to have had foot drop at the age of 16, but after wearing braces day and night for some time he recovered entirely; what this lesion was is unknown, as the man was a scoutmaster and showed no signs of peroneal atrophy when this study was made.

G II 6's oldest daughter (G III 20) had 2 sons (G IV 42 and 43), who began to have difficulty in walking when about 17 years old; by the time they were 25 both had to give up their occupations, bookkeeping and watchmaking, respectively. The only sister in the fraternity was sterilized at her own request. The other 4 daughters (G III 23 and 24) of G II 6 had no living sons, and the only living daughter (G IV 49) applied for information on birth control before her recent marriage.

G II 7 was unmarried and the keeper of the family archives at the age of 82 years; G II 8 died single at the age of 20.

G II 9 was probably normal. She had 3 daughters, the oldest (G III 27) having 3 normal boys (G IV 53), the next (G III 25) having no children and the youngest (G III 26) having 2 normal boys.

In the second generation, 7 and 10, as well as the husband of 3 and the wife of 6, were still living at ages ranging from 78 to 93. It was common knowledge that G I 5 was a crippled old bachelor. Another brother, G I 9, was reported to have been crippled, his daughters dying without issue. One sister, G I 10, left 2 normal sons who died without issue. G I 6 left no children, and G I 7 married and moved to Illinois about a century ago. Another sister (G I 11) had a crippled son. G I 4 had a niece (the mother of G II 10) who evidently transmitted peroneal atrophy to the collateral branch descending from G II 10, whose father was normal. The name of this niece's mother was lost, and the relation of her father to G I 4 was somewhat uncertain.

G II 10's oldest son (G III 28) married his kinswoman (G III 27), probably a second cousin once removed, but they had normal children and grandchildren. The second son (G III 29) was crippled and died single. The next child (G III 30), a woman of 55 years, whom I examined, had the typical atrophy of arms and hands and could not dorsiflex or evert her feet, although the muscles of the calf were good. This is evidently an example of incomplete recessiveness. Two

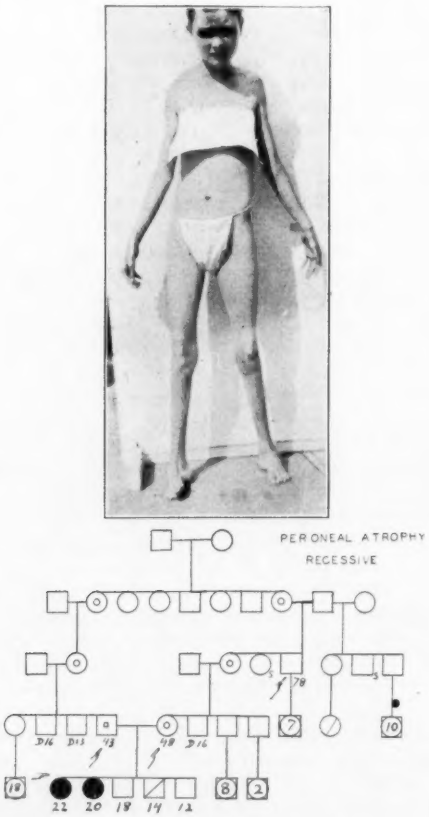


Fig. 3.—Pedigree 3 and GV 3.

(G IV 56 and 58) of this woman's 5 sons had typical peroneal atrophy. G II 10's third son (G III 31) was normal, and her other daughter (G II 32) had 2 normal sons (G IV 62).

In the first three generations of this family the majority were severely crippled, but a few continued farming throughout life. In the last two generations the age of onset has been in the second decade,

and severe disability has supervened within ten or fifteen years. The hereditary pattern is sex-linked recessive, the defective gene being in the x chromosome in the crippled man; all of his daughters receive one of these chromosomes and are carriers of the trait, passing it on to half of their sons and daughters.

PEDIGREE 3

Last spring the North Carolina Orthopedic Hospital gave me the names and photographs of 8 young girls afflicted with peroneal atrophy. These patients came from 6 separate families, and as in each family the parents were normal it was evident that the hereditary pattern must be simple recessive. So far 4 of these families have been investigated, and, as was to be expected, in each instance the parents were cousins; pedigree 3 (fig. 3), from Cabarrus County, pertains to the first of the families visited. The 2 girls G V 2 and 3, now aged 22 and 20 years, are severely crippled: Atrophy of the forearms and of the legs below the knees is extreme; the older girl began to have trouble walking at 3, the younger at 5. The photograph in figure 3 shows G V 3 at the age of 13. The parents, G IV 4 and 5, were normal but knew nothing about their family histories except that they had grandmothers with the same surname. However, they sent me to the wife's uncle, G III 6, aged 78, in another county, who gave me a much more extensive account of the first three generations than appears in the pedigree. Since 1800 there had been no other examples of peroneal atrophy within his knowledge. The parents of these children are second cousins, as will be seen from the chart.

This pedigree and the photograph illustrate the early onset and disastrous result of the disease when it is inherited as a simple recessive trait.

CLINICAL RECOGNITION OF TUBERCULOSIS OF THE MAJOR BRONCHI

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Recognition of tuberculous disease of the trachea and the major bronchi is a recent achievement in clinical diagnosis. Although it is easy to understand why older clinicians, unaided by the roentgen film and the bronchoscope, did not suspect the existence of bronchial tuberculosis, it is not clear why pathologists failed to discover the changes characteristic of the condition at autopsy. Textbooks on pathology have been strangely silent with respect to this condition, which is now frequently reported from clinical sources.

With respect to the clinical features of bronchial tuberculosis, until recently references in the literature have been meager and have usually comprised reports of single cases, such as those by Korol,[1] Neumann,[2] McConkey,[3] Crimm and Strayer,[4] Fleischner[5] and Sanes and Smith.[6] In these cases the diagnosis, although clinically suspected, was proved only by autopsy.

Progress in the diagnosis of bronchial tuberculosis and allied conditions has run parallel with the use of the bronchoscope and of bronchographic examination. The prejudice of physicians against instrumentation of the bronchi in tuberculous patients has now been overcome, and the widespread use of the bronchoscope has brought to light the existence of bronchial lesions in an unexpectedly large number of patients. Begin-

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ing in 1928, sporadic examinations of the bronchi were made by various observers, among whom may be mentioned Sproull [7] and Schonwald,[8] who were able by such examinations to confirm for the first time the clinical diagnosis of bronchial disease. Since then reports of bronchial and tracheal lesions in tuberculosis have rapidly multiplied. Careful clinical and bronchoscopic correlations have rounded out a clinical picture of this condition which is gradually being fitted into the larger panorama of tuberculous disease of the respiratory organs. Many observers have contributed to this work. The first comprehensive attempt to incorporate bronchial tuberculosis into the general framework of tuberculosis of the lungs was made by Eloesser,[9] who in 1934 published in a monograph a series of cases in which the condition was clinically diagnosed and the diagnosis proved bronchoscopically. In the same year Myerson [10] reported bronchoscopic examinations in 60 cases of tuberculosis. Since then reports of series of cases have been made by Epstein and Ornstein,[11] Myerson,[12] Phelps,[13] Samson, Barnwell, Littig and Bugher,[14] Cohen and Higgins,[15] Ornstein and Epstein,[16] Kernan,[17] Sandler [18] and Warren, Hammond and Tuttle.[19] Single cases have been reported by Werner,[20] Ballon [21] and Vinson.[22]

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(Footnotes continued on next page)

PATHOGENESIS

The manner in which the bronchi become involved in the tuberculous process is somewhat obscure. It is safe to say that isolated tuberculosis of the bronchus unassociated with older disease in the lung or in the adjacent lymph nodes does not occur. Infection of the trachea and bronchi is always secondary to some previously existing focus of tuberculosis in the chest. One of these foci has long been recognized, especially by pediatricians, who are familiar with the fatal consequences of erosion of the bronchi by adjacent caseous lymph nodes. Scobie [23] in 1934 reviewed this subject and collected reports of 94 cases, in only 19 of which recovery occurred. In adults the extension of tuberculosis from caseous lymph nodes to the bronchi is much less common. Whether the lymph nodes of adults are less caseous and more calcified than those of children or the adult bronchial tissue is more resistant, the fact remains that mechanical compression of the bronchi is more likely to occur from these adjacent caseous lymph nodes than is ulceration.

The usual source of tuberculous infection of a bronchus is an open pulmonary tuberculous lesion lying peripheral to it, and it is logical to presume that the bacilli are implanted on the mucous membrane in the same way in which they are implanted in the larynx in cases of tuberculous laryngitis. It is not plausible to assume, as some authors have done,[24] that infection occurs by contiguity from tuberculous disease of the circumjacent lung. The most extensive bronchial disease is usually found in the larger tubes at the root of the lung, in a situation where the lung tissue is relatively uninvolved. The bronchi may also be involved, as is the larynx, in any hematogenous tuberculous infection, but it is likely that the tubercles so formed play little or no role clinically; we have recently observed a case of protracted miliary tuberculosis in which the mucosa of the lower portion of the trachea and one of the major bronchi were studded with tubercles.

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PATHOLOGIC PICTURE

The pathologic character of tuberculous lesions of the trachea and bronchi warrants no detailed description here, as it differs little from that of tuberculous lesions elsewhere in the body. Tubercle formation is followed by caseation and ulceration as elsewhere, and the bronchoscope commonly discloses masses of granulation tissue, which often conceal underlying caseous or simple ulcerations. Important consequences result from penetration of the disease through the wall of the bronchus, with destruction of the cartilage. When this has occurred the bronchus can no longer maintain the patency of its lumen, and it gradually undergoes fibrous stricture with greater or less stenosis. Many of the clinical symptoms result from this narrowing of the bronchus with its mechanical effects on the lung tissue distal to it. Although physicians have become familiar with these changes through bronchoscopic studies, it must be remembered that the bronchoscope is limited in its scope by the small caliber of all but the larger bronchi. For this reason one is often in ignorance of tuberculous bronchial lesions which lie distal to an area narrowed by fibrous stricture or obstructed by granulations. In order to obtain a complete picture of the pathologic process it is necessary at times to resort to bronchographic examination, by means of which a considerable length of bronchus beyond the point of narrowing may be seen to be involved. In our experience bronchial stenosis associated with tuberculosis is never complete; although the cicatrized walls may be in apposition, a tiny lumen remains, through which secretions can find their way. One cannot, therefore, depend on the pathologic closure of a bronchus to prevent the spread of infection from the diseased lung to which it is tributary.

If one may judge from recent bronchoscopic reports, tuberculous lesions of the bronchi are far from rare, and it is likely that the routine examination of tuberculous patients would reveal a considerable number. This is indicated from the reports of Warren, Hammond and Tuttle,[19] who found 13 per cent of bronchial lesions in 90 cases in which bronchoscopic examination was done previous to thoracoplasty. In a series of 108 cases in which there were symptoms of bronchial disease, positive findings were obtained in 54 per cent. Recent autopsy studies have also shown the great frequency of bronchial lesions. Bugher, Littig and Culp[25] found such lesions in 33.6 per cent of 122 patients who died of tuberculosis. Even greater percentages are given by McConkey and Greenberg[26] who observed ulcerations in 43 of 53 autopsies.

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Since February 1935, bronchoscopic examination of all patients presenting clinical evidence of tuberculous lesions of the major bronchi has been done at the Montefiore Hospital. Twenty cases in which the clinical diagnosis was confirmed by bronchoscopic examination and in 3 of which it was also confirmed by postmortem examination are reported.

REPORT OF CASES

CASE 1.—H. H., a man aged 58, had tuberculosis of the upper lobe of the right lung. Artificial pneumothorax was induced, with resultant selective collapse. After this, smears of the sputum failed to reveal tubercle bacilli. Eighteen months later symptoms recurred and the sputum again contained tubercle bacilli. The patient came under our observation ten months later.

On being questioned, he recalled having noted wheezing arising from beneath the sternum, commencing at about the time smears showed tubercle bacilli in the sputum. Examination showed pneumothorax on the right, with selective collapse of the upper lobe; no cavities or infiltrations were seen in either lung. The trachea and the heart were in the midline.

Bronchoscopic study showed an ulceration about 1 cm. in diameter on the mesial wall of the right main bronchus; in the posterolateral branch of the bronchus to the lower lobe there was a sloughing whitish multilobular mass attached to the anterior wall. The ulcer was treated with a 35 per cent solution of silver nitrate, after which the sputum became free of tubercle bacilli, remaining so for the following five months of observation. Bronchoscopic study four months after treatment showed a depressed white scar on the mesial wall of the right main bronchus.

CASE 2.—C. S., a woman aged 25, was admitted to the Montefiore Hospital in March 1937, with pulmonary tuberculosis of four years' duration. A roentgenogram showed a cavity in the upper lobe of the right lung, for which pneumothorax had been induced, without success. There were some healed infiltrations in the apex of the left lung. Smears of the sputum showed tubercle bacilli. A two stage thoracoplasty with removal of seven ribs and liberation of the apex (method of Semb) was done. The patient improved clinically, but the sputum continued intermittently to yield tubercle bacilli. She was admitted to the Mount Sinai Hospital in February 1938. A roentgenogram showed a slit in the upper lobe of the right lung, suggestive of a cavity, but a bronchogram revealed no excavation. On bronchoscopic study granulation tissue was found in the bronchus to the upper lobe of the right lung; on microscopic examination this tissue proved to be tuberculous. After a revision operation no suspicion of cavity remained, but the sputum still intermittently contained tubercle bacilli.

CASE 3.—S. P., a woman aged 41, had pulmonary tuberculosis in 1928 (fig. 1 *A*). For the next nine years she had several exacerbations and remissions, with involvement first of the left lung, then of the right, and was a patient in several institutions. In November 1935 she first began to complain of wheezing in the left side of the chest, and a high-pitched rhonchus was heard. Examination in November 1937 revealed a loud wheeze which could be heard at a distance and which was localized to the left side of the chest. The patient was dyspneic on the slightest exertion. Breath sounds over the lower lobe of the left lung were distant, and a rhonchus was heard over the entire left lung. There was no evidence of cardiovascular disease. Smears of the sputum did not reveal tubercle bacilli. A roentgenogram showed a few calcific shadows in the lower lobe of the left lung but no significant infiltrations or cavities. In the hilus of the left lung there was a mass

which had gradually grown in intensity and size since the first film was taken in 1928 (fig. 1 *B*). Bronchoscopic examination showed the lumen of the left main bronchus to be narrowed to about 60 per cent of its normal caliber by a thin ledge on the anterior and right walls; the bronchus to the lower lobe was narrowed 50 per cent by a circular constriction of the wall. A bronchogram (fig. 1 *C*) showed two strictures of the left main bronchus. After a period of observation the patient was discharged unimproved.

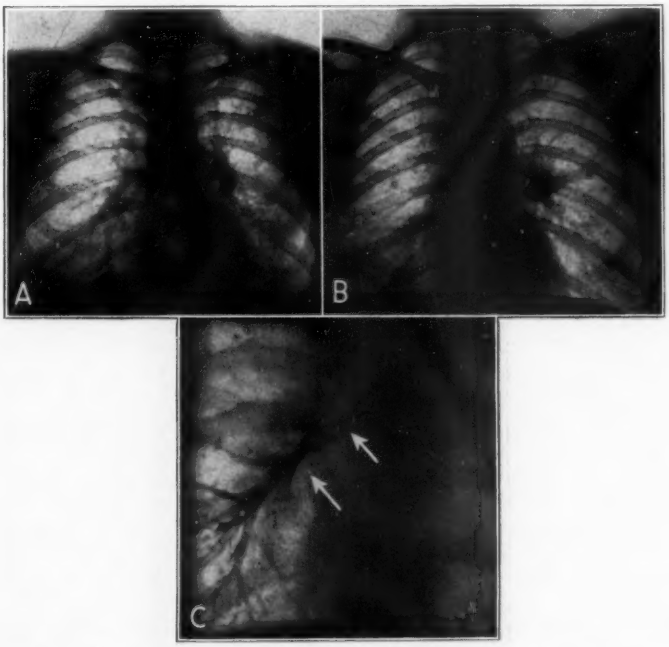

Fig. 1 (case 3).—*A*, roentgenogram taken in 1928 at the onset of the disease. *B*, roentgenogram taken in 1937. Note the increase in the size and intensity of the shadow in the left hilus and the absence of significant cavities or infiltrations. *C*, bronchogram taken in 1937, showing strictures partially occluding the left main bronchus (photograph reversed).

Case 4.—B. N., a woman aged 24, had suffered from "asthma" for many years. She would get attacks of wheezing and suffocation, which were never relieved by injections of epinephrine hydrochloride. She began to cough in 1930, and tuberculosis of the upper lobe of the left lung was found in 1931. Pneumothorax was induced, but a satisfactory collapse was not obtained and the procedure was abandoned. Despite the pneumothorax, the heart and trachea were drawn to the left (fig. 2 *A*). The intrapleural pressure was unusually low (high negative). The patient's physician suspected an intrabronchial obstruction at this time.

On admission to the hospital in January 1936 the patient still complained of intermittent wheezing. She suffered from severe attacks of choking, during which she became almost asphyxiated; lying on the right side provoked these attacks. Examination showed a large hydropneumothorax on the left, with sterile fluid; the trachea and heart were drawn to the left. Bronchoscopic examination showed the trachea to be narrowed at its lower portion; the left main bronchus was completely occluded, except for a small lumen about 2 mm. in diameter, by dense scar

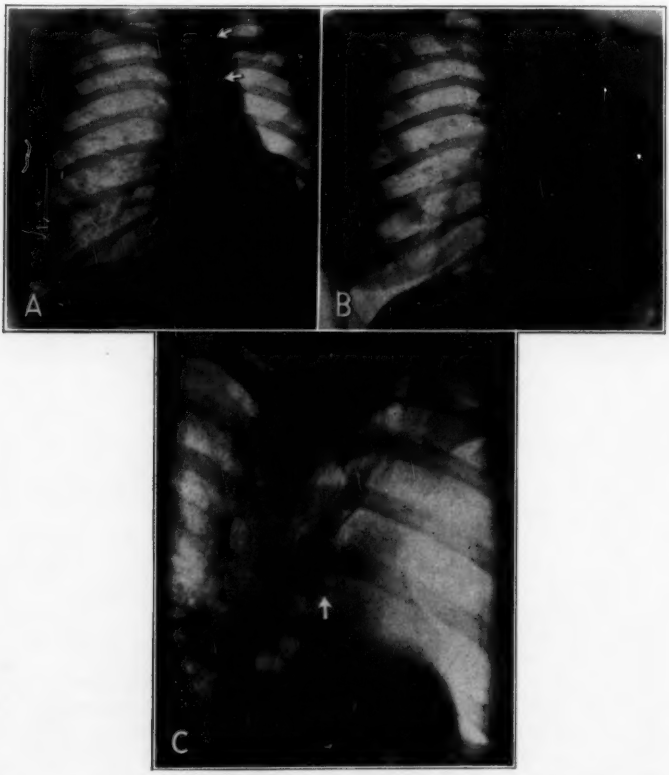

Fig. 2 (case 4).—*A*, roentgenogram taken in June 1935. Despite pneumothorax, the trachea (arrows) and the heart are pulled to the left. *B*, roentgenogram taken in January 1937, after discontinuation of pneumothorax, showing atelectasis of the left lung. *C*, bronchogram showing the left main bronchus reduced to a small slit.

tissue. Bronchographic study (fig. 2 *C*) showed the left main bronchus reduced to a small slit, ending in a blind pouch ½ inch (1.2 cm.) from the bifurcation. During the patient's stay in the hospital the sputum became free of tubercle bacilli. The left pleural space was gradually obliterated, with retraction of the heart and

trachea far to the left and narrowing of the intercostal spaces on that side (fig. 2 *B*). When last seen, in March 1938, the patient still suffered from severe attacks of dyspnea and wheezing; she had a new lesion in the right lung, and smears of the sputum again showed tubercle bacilli.

CASE 5.—I. K., a woman aged 28, was found to have a tuberculous lesion of the upper lobe of the right lung in February 1935. Artificial pneumothorax resulted in symptomatic improvement for ten months, after which cough reappeared and she noted wheezing from the center of the chest; she expectorated a number of "bronchial casts." Smears of the sputum revealed tubercle bacilli. Bronchoscopic study at another hospital showed the right main bronchus to be constricted by a mass of rough, friable tissue; there was an ulceration of the bronchial wall, which extended up into the trachea, and purulent material was obtained from beyond the constriction. The patient was then followed in the outpatient department of the Lenox Hill Hospital for a year, during which time the sputum contained no tubercle bacilli. Dyspnea and wheezing would reappear, and a refill would give relief. Every two weeks the stricture was dilated and a solution of silver nitrate was applied to the ulcer. The last bronchoscopic examination, in October 1937, showed the lumen of the right main bronchus to be reduced to about ⅛ inch (0.32 cm.) in diameter by a circular smooth scar. Smears of the sputum began to show tubercle bacilli about this time, and the patient was admitted to the Montefiore Hospital in November.

Examination showed pneumothorax on the right with about 60 per cent collapse of all lobes; the heart and trachea were drawn to the right. Numerous smears of the sputum failed to disclose tubercle bacilli. The intrapleural pressure was very low. The patient would not give permission for bronchoscopic and bronchographic examinations and was discharged soon afterward in relatively good condition. In May 1938 her general condition was unchanged.

CASE 6.—B. M., a woman aged 27, had tuberculosis of the left lung in April 1935. Pneumothorax was induced at the New York State Hospital at Ray Brook, N. Y. The sputum, however, persistently showed tubercle bacilli in smears. Persistent bronchial rales were heard over the upper lobe of the left lung, which caused a bronchial lesion to be suspected. The patient was transferred to the Montefiore Hospital in October 1936.

She had never noted wheezing. Examination showed pneumothorax on the left; the collapsed lung shadow was rather dense and homogeneous, and the trachea and heart were in the midline. The sputum contained tubercle bacilli. In the next few months a large amount of fluid appeared in the left pleural cavity; this fluid was always clear and sterile. Bronchoscopic study in March 1937 showed the lumen of the left main bronchus at the level of the orifice of the branch to the upper lobe to be narrowed to about one-half its normal diameter. The lateral wall was ulcerated and covered with a whitish exudate, and the bronchus to the upper lobe was narrowed by a similar ulcerostenotic process. Biopsy showed tuberculous granulation tissue.

In the course of the next two months the fluid gradually absorbed. The heart and trachea were drawn far to the left. The patient returned to the care of her private physician, who in March 1938 reported that there had been little change. There was occasional wheezing from the left side of the chest, and rhonchi could be heard on this side. She declined to reenter the hospital for further treatment.

Case 7.—R. F., a woman aged 33, first had pulmonary symptoms in 1934. On her admission to the country sanatorium of the Montefiore Hospital in April 1935, examination showed a minimal lesion of the upper lobe of the right lung. Smears of the sputum revealed tubercle bacilli. A small triangular shadow was seen in the right paratracheal region (fig. 3 *A*). The shadow became larger and denser until, in September, it assumed definitely the appearance of an atelectatic lobe (fig. 3 *B*). The patient refused to permit bronchoscopic study. Pneumothorax was induced, but collapse was hindered by several adhesions. Refills were given at intervals during the next two years, but the state of the patient's health was only fair, and tubercle bacilli were alternately present and absent in smears of the sputum.

The patient was admitted to the Montefiore Hospital in September 1937. She had never detected a wheeze, nor were rhonchi heard. A roentgenogram showed partial pneumothorax on the right. The trachea and heart were in the midline but were drawn somewhat to the right on inspiration. Bronchoscopic study showed

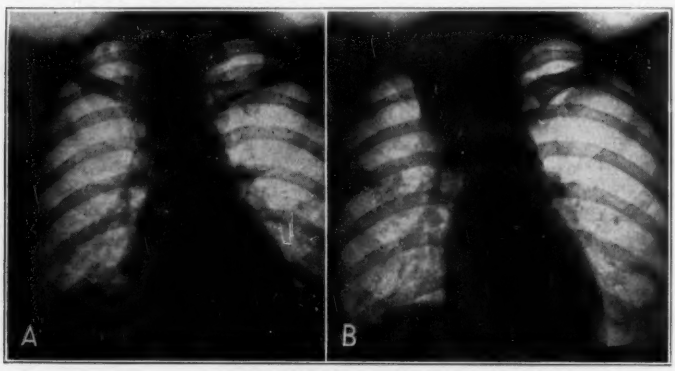

Fig. 3 (case 7).—*A*, roentgenogram taken April 30, 1935. Note the small shadow in the right paratracheal region. *B*, roentgenogram taken on September 14. The shadow has become larger, indicating atelectasis of the upper lobe of the right lung.

the main bronchus of the right lung to be almost completely obstructed just below the bifurcation of the trachea by a smooth area of stenosis with an apparently intact mucosal surface; below this area of stenosis there was visible for a short distance a ragged bronchial wall which narrowed the lumen and was covered with slough and thick secretion. Biopsy showed tuberculous granulation tissue. The patient requested discharge from the hospital and when last heard from was in Colorado.

Case 8.—E. W., a woman aged 29, had pulmonary tuberculosis in 1931. A roentgenogram taken in 1933 showed a triangular shadow in the right parasternal region; the trachea and heart were in the midline. She was admitted to the hospital in December 1934. Dyspnea was marked. Physical signs were not remarkable. The parasternal shadow was still present (fig. 4 *A*). The sputum contained tubercle bacilli. Pneumothorax was induced in February 1935. In July the patient complained of a "raw sensation in the bronchi," and an expiratory stridor to the right of the sternum was detected. The intrapleural pressure at this time

was somewhat low. She had high fever and appeared acutely ill. In the latter part of 1935 a dense shadow appeared in the upper portion of the right lung field, gradually progressing over the entire side. Pneumothorax was discontinued, whereupon the heart and trachea shifted markedly to the right (fig. 4*B*). Bronchoscopic study in March 1936 showed the right main bronchus to be narrowed from its orifice downward by protrusion inward of the lateral wall, which was covered with exudate. The patient's condition became progressively worse. Dyspnea and wheezing were intense. The left lung became involved. Death occurred in August 1936.

Autopsy showed the right lung to be reduced to a mass 10 cm. in diameter, which did not contain air but did contain a few irregular cavities. The mucosa of the right main bronchus was reddened, thickened and piled up in corrugated fashion; several areas appeared ulcerated. Microscopic examination showed the bronchial wall to be extremely thickened by dense hyalinized fibrous tissue. Tubercles were seen in the submucosa.

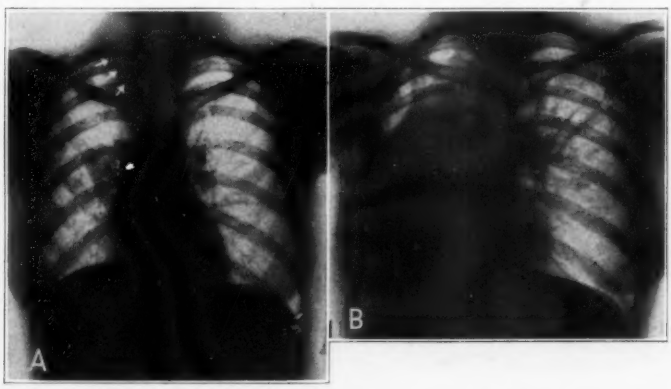

Fig. 4 (case 8).—*A*, roentgenogram taken in December 1934. Note the triangular paratracheal shadow. B, roentgenogram taken in February 1936. There is atelectasis of the right lung.

Case 9.—J. P., a woman aged 30, was admitted to the Montefiore Hospital in August 1935 with pulmonary tuberculosis of at least three and one-half years' duration. A roentgenogram showed a shadow in the right paratracheal region suggestive of atelectasis of the upper lobe. The heart was pulled slightly to the right. Bronchoscopic study showed the orifice of the bronchus to the upper lobe of the right lung to be represented by a dimple. A bronchogram showed a small blind pouch protruding from the right main bronchus at the level of its bifurcation; the apical branch of the lower lobe bronchus supplied the area normally in the position of the upper lobe.

There were several exacerbations and remissions of the disease. The paratracheal shadow persisted. In 1936 a cavity appeared in the upper part of the right lung field. Pneumothorax was induced. During this period the patient detected wheezing over the right side of the chest; a loud rhonchus was heard in the right parasternal area. After section of the adhesions the sputum became

free of tubercle bacilli. The collapsed upper lobe was pictured in the roentgenogram as a small dense triangular shadow; the heart and trachea were drawn slightly to the right. At the time of writing pneumothorax treatment is being carried out in the outpatient department, and the patient is feeling well.

CASE 10.—R. M., a woman aged 20, entered the country sanatorium of the Montefiore Hospital in December 1935. At this time a roentgenogram showed mottling throughout the right lung. Pneumothorax was induced; good collapse was obtained and the sputum soon became free of tubercle bacilli. About six months later (October 1936) it again showed tubercle bacilli, and at about this time the patient noted a wheeze coming from the right side of the chest. Pneumothorax was maintained. During the first five months of 1937 the collapsed upper lobe gradually began to shrink, so that by May it appeared roentgenographically as a dense triangular shadow (fig. 5 *A*); the trachea and heart were only slightly pulled to the right. Bronchoscopic examination in November 1937 showed the bronchus to the upper lobe of the right lung to be pushed downward; the lumen was narrowed, and the mucosa was congested and bled easily. A specimen taken for

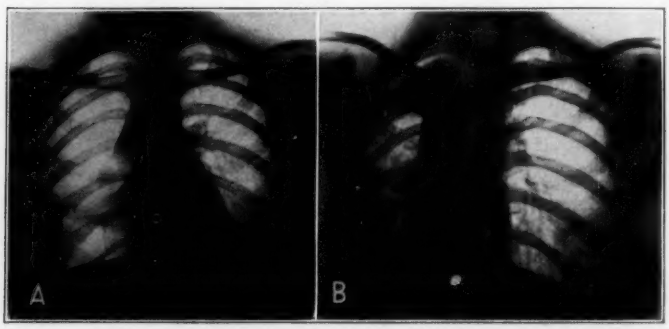

Fig. 5 (case 10).—*A*, roentgenogram taken in May 1937, during the course of pneumothorax treatment. The dense triangular shadow represents the atelectatic upper lobe of the right lung. *B*, roentgenogram taken in March 1938, after discontinuation of pneumothorax treatment. Collapse of the upper lobe of the right lung has persisted. The heart and the trachea are drawn to the right, suggesting beginning obstruction of the main bronchus.

biopsy showed tuberculous granulation tissue. Pneumothorax was discontinued in January 1938. The patient's condition remained good. The sputum was mostly free of tubercle bacilli, but occasionally a smear showed these organisms. Wheezing became less frequent. After discontinuation of the pneumothorax the lower and the middle lobe of the right lung gradually expanded, pushing the atelectatic upper lobe upward (fig. 5 *B*). The heart and trachea were drawn further into the right side of the chest, and the interspaces became very narrow; we suspected from this that occlusion of the main bronchus was occurring. In May there was sudden severe hemoptysis, followed by spread of the disease to the lower lobe of the right lung and a constitutional reaction. The sputum began constantly to yield tubercle bacilli.

CASE 11.—I. S., a woman aged 62, was admitted to the Montefiore Hospital with pulmonary symptoms of three years' duration. She was emaciated. The left

side of the chest was flat. There was dulness over the entire upper lobe of the left lung, with distant bronchial breathing and numerous rales. A roentgenogram showed a dense shadow, sharply demarcated, occupying the site of the upper lobe. Bronchoscopic study showed the left main bronchus to be narrowed by moderately soft fibrous tissue; a slit remained, which could be dilated to 4 mm. A bronchogram showed the bronchus to be narrowed, apparently by pressure from without.

The course was progressive. Extensive bilateral cavitation occurred, and the patient died seventeen months after her admission to the hospital. Autopsy showed the left lung to be one-half the size of the right. The upper lobe was airless and contained several cavities. The lower lobe was emphysematous, nodular and fibrotic. The left main bronchus was reduced to a slit. A large, partly calcified lymph node in the infratracheal region seemed to compress the bronchus. The peripheral bronchi were dilated. Microscopic study of the bronchial wall showed large amounts of hyalinized fibrous tissue around the cartilages. Tubercles were seen in the submucosa. No epithelium could be observed.

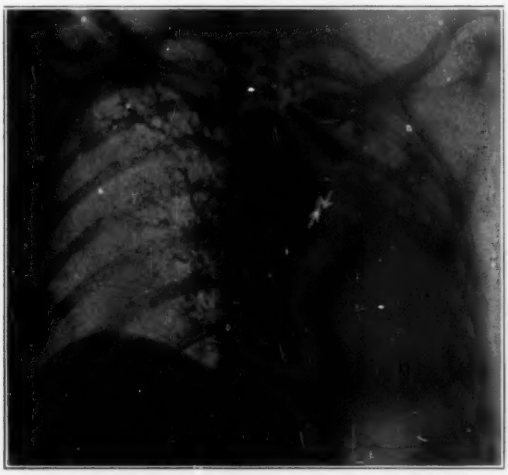

Fig. 6 (case 12).—Bronchogram showing a stricture of the left main bronchus.

CASE 12.—R. K., a woman aged 37, was found to have tuberculosis of the left lung in 1935. Pneumothorax was induced elsewhere, and she was admitted to the Montefiore Hospital in September. Examination showed hydropneumothorax on the left; the heart and trachea were pushed to the right. The fluid became purulent, and pneumothorax was discontinued. The pleural cavity gradually obliterated itself, and early in 1937 the mediastinum began to shift to the left. In March the patient detected wheezing from the left side of the chest, and an inspiratory rhonchus was heard over the left paravertebral region. The left lung field became dense. Bronchoscopic examination in November showed the left main bronchus to be occluded 1.5 cm. below the bifurcation by a firm, fibrous stricture, a lumen about 3 mm. in diameter being left. Bronchographic examination showed a partial stricture of the bronchus (fig. 6).

CASE 13.—B. P., a woman aged 22, was found to have tuberculosis of the upper lobe of the right lung in 1934. Pneumothorax was attempted and abandoned. In 1936 she detected a wheeze arising from beneath the sternum; this appeared intermittently. She was admitted to the Montefiore Hospital in August 1937. On examination a rhonchus was heard over the right paravertebral region. In the ensuing three months the right lung field became dense; the interspaces became narrow, and the heart and trachea moved into the right side of the chest (fig. 7). Bronchoscopic examination revealed the carina to be thickened, with resultant

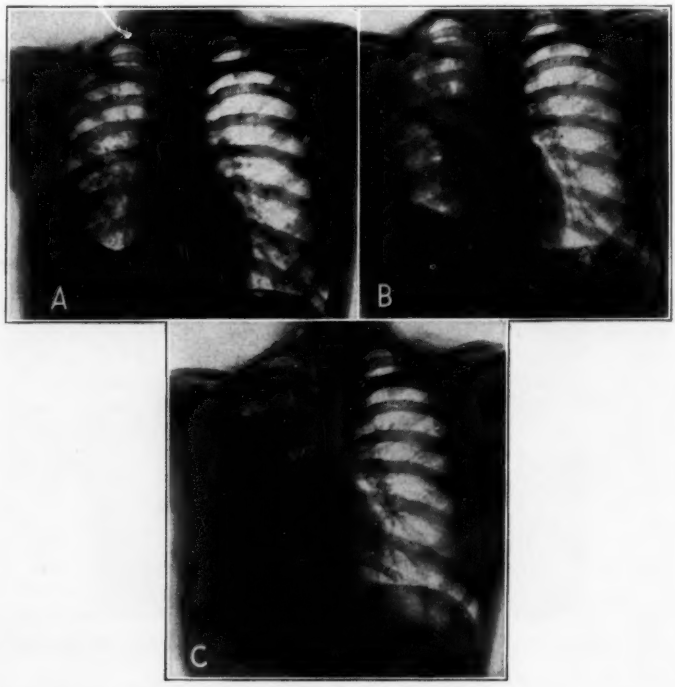

Fig. 7 (case 13).—*A*, roentgenogram taken in July 1937. No evidence of atelectasis is present. *B*, roentgenogram taken one month later. The mediastinum is beginning to shift to the right. *C*, roentgenogram taken four months later. There is further progression of the atelectasis.

narrowing of the orifice of the left main bronchus. The right main bronchus was completely occluded by swelling of the mucosa and obstruction of the residual lumen by slough and pus; on removal of this secretion the lumen was about 5 mm. in diameter, and extensive ulceration of the wall was seen. Bronchographic study showed the right main bronchus to be reduced to about one quarter of the normal caliber. The bronchus to the upper lobe was somewhat narrowed and

communicated with a large series of cavities. All that could be seen of the middle and lower lobe bronchi was a stem bronchus about ¾ inch (1.9 cm.) long, ending in a few ectatic sacculations.

CASE 14.—B. G., a woman aged 30, was admitted to the Montefiore Hospital in August 1934 with a three year history of pulmonary symptoms marked by hemoptysis on numerous occasions. Physical examination showed dulness over the entire left lung. Smears of the sputum disclosed tubercle bacilli. A roentgenogram showed a dense homogeneous shadow over the entire left lung; a large cavity with a fluid level apparently within lung tissue was noted in the upper portion of the lower lobe of the left lung; the trachea and heart were retracted to the left. Pneumothorax was induced, but numerous adhesions prevented satisfactory collapse.

The patient's condition remained unchanged, but the sputum gradually became free of tubercle bacilli. In 1937 an inspiratory and expiratory rhonchus was heard over the left side of the chest. Bronchoscopic study showed a stricture of the left main bronchus above the orifice of the bronchus to the upper lobe; the lumen was narrowed to about 3 mm.; the mucosa seemed intact; there was also kinking of the main bronchus below the stricture, so that practically no aeration of the lung was obtained unless the bronchus was straightened.

CASE 15.—B. G., a woman aged 40, had pulmonary tuberculosis in 1910 and had spent five years in several hospitals, after which the disease was considered arrested. Exacerbation of the symptoms led to her admission to the Montefiore Hospital in July 1934. Examination showed retraction of the entire left side of the chest; there were flatness and distant breath sounds over the left lung. A roentgenogram showed a dense shadow over the left lung field; the interspaces were narrowed; the heart and trachea were drawn to the left. Bronchoscopic study showed the left main bronchus to be narrowed to a diameter of 2 mm. about 2 cm. below the carina; the mucosa was red and granular. Bronchographic study (fig. 8) showed the main bronchus to end in a blind pouch 2.5 cm. below the bifurcation. Aspiration of the left pleural cavity yielded thick pus; a bronchopleural fistula was demonstrated. Symptoms of mental disease subsequently developed, and the patient was discharged to a psychiatric institution.

CASE 16.—J. P., a woman aged 64, had hoarseness and cough four years prior to her admission to the hospital. Nine months previously she was treated for "pneumonia" of the upper lobe of the right lung and was in bed six weeks. Cough and expectoration persisted, and she was admitted to the Montefiore Hospital in December 1937.

She stated that she had had "asthma" twelve years before but that it had gradually disappeared. She had noted its return during the previous year. On physical examination she was dyspneic on the slightest exertion. A wheeze could be heard at some distance; this she localized to the right side of the chest. There were dulness and distant breath sounds over the middle lobe of the right lung, where a loud inspiratory rhonchus was heard. Roentgen examination (fig. 9) showed a triangular shadow corresponding to an atelectatic middle lobe; there was no shift of the mediastinum. Repeated examinations of the sputum failed to reveal tubercle bacilli.

Bronchoscopic study showed creamy pus coming from the upper lobe of the right lung. On the mesial wall of the right main bronchus, opposite the orifice of the branch to the lower lobe, a thickened, healed ulceration was seen, in the

Fig. 8 (case 15).—Bronchogram showing the left main bronchus ending in a blind pouch.

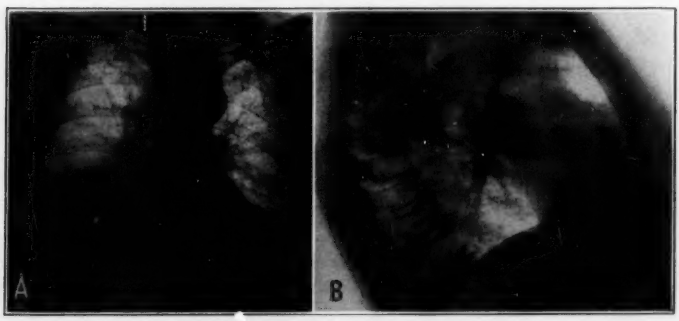

Fig. 9 (case 16).—*A*, atelectasis of the middle lobe of the right lung. *B*, lateral view.

midst of which there was an area of anthracotic pigmentation 6 mm in diameter. Below this the bronchus was narrowed so that the instrument could not be passed; the bronchus to the middle lobe appeared completely occluded by scar tissue. After bronchoscopic examination the patient became dyspneic and required oxygen therapy. Physical and roentgen examination indicated atelectasis of the lower lobe of the right lung. The symptoms and signs cleared, and in the course of a week the original picture was restored. Bronchographic study showed a small anterior radicle of the right main bronchus, which lay in the position normally occupied by the bronchus to the middle lobe of the lung; there a small collection of iodized poppyseed oil was seen, and the bronchus terminated ¼ inch (0.64 cm.) from its point of origin.

CASE 17.—B. F., a woman aged 59, was admitted to the Beth Israel Hospital in April 1936, complaining of fever, cough and pain in the right chest of two weeks' duration. On the day of admission she had noted some blood-streaked sputum. She had suffered from "bronchial asthma" for eighteen years and was supposed to be sensitive to feathers. On examination she appeared acutely ill. The temperature was 104 F. The respirations were rapid and shallow. She was moderately cyanosed. There were dulness and suppressed breath sounds over the lower part of the right lung. Numerous musical rales were heard throughout both lungs. The sputum did not contain tubercle bacilli. The temperature fell to about 100 F. in a few days. Roentgenograms showed complete lack of aeration of the lower and the middle lobe of the right lung; the trachea and heart were in the midline. Bronchoscopic study on April 24 showed the carina to be somewhat thickened; at a level just below the orifice of the bronchus to the upper lobe the medial and anterior walls of the main bronchus showed thickened mucosa, forming an area of stenosis. There were several anthracotic-appearing areas studding it. Biopsy failed to reveal tumor or tuberculous tissue. It was nevertheless felt that the patient was suffering from a neoplasm. She was given high voltage roentgen therapy. Little improvement was noted, and she was discharged twelve weeks after admission.

After her discharge from the hospital, the cough persisted. Otherwise she felt well. No wheezing was noted. She was readmitted for further study in December 1937. Examination showed atelectasis of the middle and the lower lobe of the right lung; there were deviation of the trachea to the right and slight elevation of the right half of the diaphragm. The sputum was sterile. Bronchoscopic study on December 21 showed the bronchus to the upper lobe of the right lung to be narrowed to one-half its normal caliber; at a point 0.5 cm. below the orifice of this bronchus the main bronchus was stenosed in a funnel arrangement, with a reduction in caliber to about 3 mm.; at this point numerous anthracotic spots studded the mucous membrane. A specimen taken for biopsy revealed no significant lesion.

CASE 18.—G. H., a man aged 70, had cough and hemoptysis in 1931. Roentgen examination at another hospital showed a dense, irregular shadow in the midportion of the lung; the intercostal spaces were narrowed, and the heart was drawn to the right. It was felt that the patient was suffering from bronchogenic carcinoma, and intensive roentgen therapy was given. He continued to suffer from cough, hemoptysis, pain in the right side of the chest and loss of weight and was admitted to the Montefiore Hospital in December 1934. Physical and roentgen findings indicated atelectasis of the entire right lung, with marked shrinkage of the hemithorax. A roentgenogram showed several calcified areas in the

Fig. 10 (case 18).—Shrinkage of the entire right side of the chest, due to atelectasis. The arrows point to calcified areas in the hilus of the right lung, representing lymph nodes. The upper of these is probably in the main bronchus.

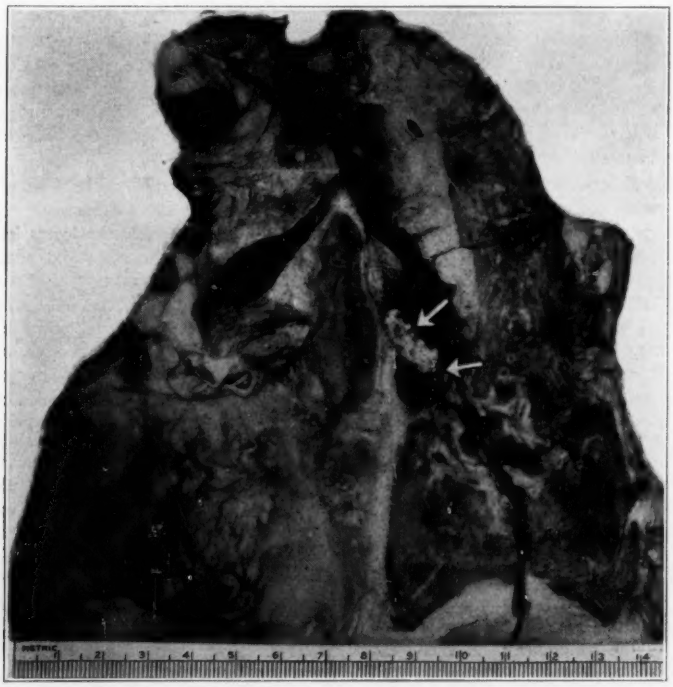

Fig. 11 (case 18).—Postmortem specimen. The posterior view of the heart and the right lung is shown. Note the calcified lymph node breaking into the main bronchus.

right hilar region (fig. 10). Smears of the sputum did not reveal tubercle bacilli. Bronchoscopic study showed the right main bronchus to be almost completely occluded; the impression was that a foreign body was present. It was planned to repeat the bronchoscopic examination, but the poor condition of the patient prevented it, and he died three weeks later.

Autopsy showed the left lung to be voluminous. The right lung was shrunken and airless. The right main bronchus just behind the bifurcation contained a hard body encrusted with calcium salts, which eroded and perforated the bronchial wall (fig. 11). This obviously was a lymph node which had perforated into and occluded the bronchus.

CASE 19.—M. W., a man aged 26, consulted one of us (H. W.) in December 1930. Nine years previously he began to have hemoptysis. A diagnosis of pulmonary tuberculosis was made, and the patient had since been treated in various institutions. Examination showed involvement of the apex of the left lung. A roentgenogram showed displacement of the trachea to the left; the bronchus of the upper lobe of the left lung was deformed, narrowed and displaced downward by a mass just outside it, which resembled a large lymph node. Bronchoscopic study revealed a superficial ulceration on the floor of the left main bronchus near the orifice of the branch to the upper lobe of the lung. Phrenicotomy resulted in temporary improvement, but when the patient was seen in March 1936, there was progression of the lesion in the apex of the left lung. He continued to have mild hemoptysis from time to time.

CASE 20.—H. C., a man aged 44, was first admitted to the country sanatorium of the Montefiore Hospital in February 1928. Physical signs were not remarkable. The sputum yielded bacteria on culture. A roentgenogram showed a large round cavity in the apex of the left lung (fig. 12 *A*). The patient was discharged and was admitted subsequently a number of times, without any significant change in his condition. When he was admitted to the hospital in February 1934, however, it was found that the site of the cavity in the apex of the left lung was occupied by a dense homogeneous shadow; a new, larger cavity was present below it (fig. 12 *B*). This picture was interpreted as indicating blockage of the tributary bronchus. Bronchoscopic examination on Sept. 17, 1935, showed the bronchus to the upper lobe of the left lung to be narrowed; the lumen of its paravertebral branch was reduced to a slit. Bronchographic study showed the apical branches of that bronchus to be occluded just below the obliterated cavity (fig. 12 *C*).

COMMENT

A study of the cases presented indicates knowledge has progressed so that bronchial tuberculosis can be clinically diagnosed. It is well to bear in mind, however, certain circumstances which stand in the way of early diagnosis. The mere presence of ulcerations or of stenosis of the bronchi does not mean that there will be characteristic or even suggestive symptoms of this condition. The bronchi in the presence of a long-standing pulmonary disease like tuberculosis may be insensitive to inflammatory changes of the mucous membranes. It is also known

from experience with tumors of the bronchi that gross organic lesions may be symptomless for long periods. One cannot avoid the conclusion that tuberculous bronchial lesions may be latent for a considerable time when one observes through the bronchoscope the occlusion of a bronchus in a patient in whom this condition had not been suspected. Furthermore, in most cases there is little or nothing in the character of the

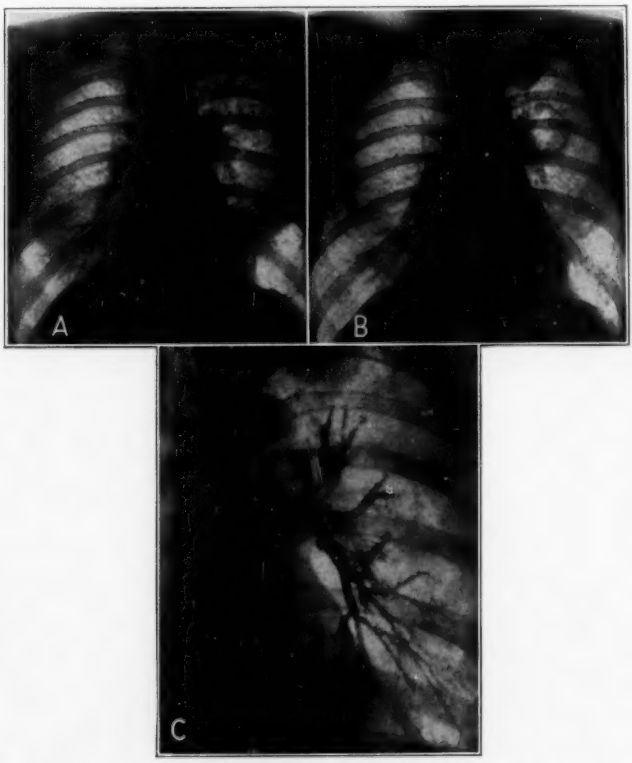

Fig. 12 (case 20).—*A*, roentgenogram taken in February 1932. Note the large cavity in the upper lobe of the left lung. *B*, roentgenogram taken in May 1934. Note the cavity filled with radiopaque substance. *C*, bronchogram showing the apical branches occluded below the obliterated cavity.

cough or the expectoration which permits one to say that a bronchial factor has been added to the pulmonary disease already present.

Case 1 represents perhaps the simplest combination of symptoms which may arouse a suspicion of bronchial tuberculosis. The patient

had no cough or expectoration, and an effective therapeutic collapse of the lung left him with sputum which contained tubercle bacilli. Under these circumstances experience would warrant one to expect the sputum to be free from tubercle bacilli. Obviously the cause of this condition had to be sought elsewhere than in an open cavity, of which there was no evidence. On bronchoscopic examination a tuberculous ulcer of a main bronchus was found, from which tubercle bacilli were freely discharged. A similar explanation will apply to cases in which thoracoplasty is done and in which examination of the sputum continues to show tubercle bacilli in spite of the fact that the cavity has been adequately collapsed. This is well illustrated in case 2.

The only symptoms which may be regarded as characteristic of bronchial tuberculosis are those which result from a decrease in the caliber of the trachea or of a large bronchus. Such structural changes, impeding the passage of air into the lungs, are manifested by symptoms which have positive diagnostic value. The cases here reported illustrate most of these, which may be both subjective and objective. As they are the result of the same mechanical changes, they complement each other, so that taken together they are in many cases pathognomonic.

Among the subjective symptoms there is one which occurs with such frequency that it may be considered characteristic, namely, a wheezing sound which is usually noted by the patient as well as by the examiner. It is surprising how long a patient may have been aware of this sign without attributing any significance to it or calling it to the attention of the physician. This wheeze or rhonchus is usually low pitched and sonorous and in its most significant form is constantly present owing to a fibrous stricture of a large bronchus. However, it may appear only when granulations or mucus are lodged in a narrowed bronchus. For this reason even an inconstant sonorous rhonchus may have significance if it is always heard over the same point on the wall of the chest. When it is sufficiently loud it is heard all over the chest, although its maximum intensity is usually over the affected bronchus, and it is often so localized by the patient. When the caliber of the bronchus is contracted beyond a certain point there is a progressive decrease in the intensity of the rhonchus, until it finally disappears.

As obstructive lesions are commonly found in the main or lobar bronchi, the objective symptoms of this condition arise from the collapse of a whole lung or one of its lobes, with resulting alteration of the normal pressure relations in the chest. These changes are clearly shown

in patients in whom the lung has already been collapsed by therapeutic pneumothorax. Whenever during the course of such treatment a lobe of the lung exhibits extreme collapse without any tendency to reexpand when pneumothorax is suspended (case 10) it is proper to suspect that there may be an obstruction of the bronchus. This suspicion will find support when, in addition, a rhonchus is audible.

In this series of cases the lesion occurred most commonly in a main bronchus. In only 9 was the obstruction so complete as to result in the collapse of a whole lung. In a tenth case of obstruction of the main bronchus there was atelectasis of a single lobe (case 11). In all the other cases of lobar atelectasis, of which there were 5, the main bronchi were free of disease, the obstructive lesion involving only the lobar bronchus, which was always in the upper lobe. It is important to note that the collapse of a single lobe cannot readily be determined without roentgen examination, because it is not followed by noticeable displacement of the mediastinum. In some cases (7 and 8) the progress of a lesion from a lobar to a main bronchus could be observed by its effect on the aeration of an increasing part of the lung and by a marked shift of the mediastinum. When pneumothorax was maintained this transition was marked by a fall in intrapleural pressure.

Naturally, the respiratory function will at times be profoundly disturbed under these conditions, although the mechanism of this change is not always clear. Attacks of dyspnea similar to asthma may occur, which obviously cannot be due to closure of a single bronchus. In analysis of the cause of dyspnea in such cases other factors, such as extensive tuberculous disease of the opposite lung, must be considered. The closure of a main bronchus under these conditions would reduce the respiratory area of the whole lung field to a critical level. It will also be found in some cases that the respiratory difficulty is aggravated by the mediastinal displacement which follows massive collapse of a whole lung. In such a case (case 5) it was possible to reestablish almost normal breathing by giving refills under moderate pressure, which restored the mediastinum to its median position. In 1 instance (case 4) the patient suffered attacks of air hunger bordering on asphyxia when she assumed certain postures. This could be explained by a marked narrowing of the lower portion of the trachea, which, added to a complete stricture of one of the main bronchi, compromised the air passage to an extreme degree.

The influence of tuberculous disease of the lymph nodes on the adjacent bronchus merits some consideration. It is true that, especially

in adults, the symptoms and pathologic changes due to intrinsic tuberculous disease of the bronchi do not commonly result from the presence of enlarged tuberculous lymph nodes. However, there is ample evidence that such nodes may compress and erode neighboring structures with serious consequences to the bronchi, the pulmonary blood vessels and the lungs.

In young children the rupture of caseous lymph nodes into a bronchus has long been recognized; it occupies an important place in the pathogenesis of acute tuberculous pneumonia. The clinical symptoms due to pressure of large lymph nodes, especially in the paratracheal region, have been described by various authors (Sluka,[27] Rach[28]), who have drawn attention to the inspiratory stridor which results from pressure on the lower end of the trachea. Atelectasis of various lobes of the lung has resulted from such pressure, the effects of which may be permanent. It has even been suggested that so-called epituberculous infiltration in young children is not actually infiltration of the lung by disease but is a condition due to atelectasis of portions of the lung caused by the pressure of enlarged tuberculous lymph nodes at the hilus (Rössle,[29] Brock and others[30]).

In adults it appears that the rigidity of the larger bronchi is usually an obstacle to complete occlusion of a main bronchus by pressure of tuberculous nodes. With increasing age, also, the lymph nodes become anthracotic and indurated and contain less caseous material, so that the tendency to ulcerate into the larger bronchi is not so great. For this reason tuberculous bronchopneumonia due to this cause is undoubtedly much less frequent in adults than in children. In this series 1 patient showed gradual bronchial occlusion despite clearing of all pulmonary infiltrations. Over a period of nine years the roentgenograms showed gradual enlargement and intensification of a shadow in the hilus of the left lung, doubtless representing lymph nodes (case 3, fig. 1). In another case of bronchial occlusion autopsy showed a large, partly calcified lymph node which appeared to compress the bronchus (case 11). In a third case (case 20), clinically considered one of bronchial carcinoma, a calcified lymph node was observed at autopsy which had perforated into and completely occluded the right main bronchus. We

27. Sluka, E.: Ueber Röntgenbefunde bei tuberkulösen Kindern mit expiratorischem Keuchen, Wien. klin. Wchnschr. **23**:136, 1910.

28. Rach, E.: Zur Klinik der Bronchialdrüsentuberkulose im Kindesalter, Beitr. z. Klin. d. Tuberk. **32**:31, 1914.

29. Rössle, R.: Die pathologisch-anatomische Grundlagen der Epituberkulose, Virchows Arch. f. path. Anat. **296**:1, 1935.

30. Brock, R. C.; Cann, R. J., and Dickinson, J. R.: Tuberculous Mediastinal Lymphadenitis in Childhood: Secondary Effects on the Lungs, Guy's Hosp. Rep. **87**:295, 1937.

have observed a number of cases not recorded here in which the bronchoscopist could demonstrate narrowing of the bronchi by pressure of large nodes without any change in the mucous membranes.

The relation of tuberculous lesions of the bronchi to hemoptysis is of some clinical interest. Ulcerations and tuberculous granulations do not seem, as a rule, to give rise to severe hemoptysis. On the other hand, we have observed a number of cases in which repeated severe hemoptysis was associated with the pressure of tuberculous nodes on the major bronchi. On bronchoscopic examination the larger bronchi showed marked compression; there was congestion of the mucous membrane without any actual invasion of the bronchial walls by the tuberculous process. The nodes may at times be recognized in the roentgenogram, especially when they form clearly outlined masses in the recess between the trachea and the main bronchi. In other cases calcification of many nodes, with or without the expectoration of broncholiths, has been associated with severe hemoptysis recurring during a period of years. It is important to bear in mind that severe and fatal hemorrhage from the lungs may follow simultaneous erosion of a branch of the pulmonary artery and of the bronchial wall. This has been especially noted with older patients, in whom the only evidence of previous pulmonary disease was an anthracotic, indurated lymph node. The slow extension of the caseous center of such a node to the neighboring pulmonary artery and the bronchial wall led to rapidly fatal hemorrhage in 10 cases reported by Arnstein.[31] In this connection it is of interest that Vinson and Toone [32] recently reported a case of unexplained hemoptysis, in which they found an anthracotic lymph node protruding into the lumen. Cases 16 and 17 of this series are included in spite of the fact that neither patient showed evidence of preexisting or coexisting tuberculosis. In each case the picture was that of lobar atelectasis, and bronchoscopic study showed bronchial occlusion with anthracotic pigmentation at the site of obstruction, suggesting antecedent perforation by lymph nodes.

Recently Fleischner [5] and Neumann [2] reported further evidence of the influence of tuberculous nodes on the thoracic organs other than the bronchi. Adhesion of these nodes to the esophagus is likely to produce small traction diverticula which are easily demonstrable in the roentgenogram (fig. 13). In 7 cases of this series in which the esophagus was studied with the aid of barium sulfate, diverticula were found in 2 (1 and 12). In at least 8 of our cases there is thus some evidence that hilar lymph nodes played a pathogenic role.

31. Arnstein, A.: Ueber indurierende Bronchialdrüsentuberkulose als Ursache schwerer Hämoptoe bei älteren Leuten, Beitr. z. Klin. d. Tuberk. **78**:55, 1931.

32. Vinson, P. P., and Toone, E. C.: Pulmonary Symptoms Resulting from Ulceration of Hilar Nodes into a Bronchus, West Virginia M. J. **33**:200, 1937.

Prognosis.—Since this syndrome has been recognized for only the past few years, insufficient time has elapsed for a proper evaluation of its role in prognosis. The impression to be gathered from previous reports is that patients with this complication usually do poorly. From our experience in this series, in which patients have been followed from one to four years after onset of symptoms, we agree with this impression. At the time of writing, only 1 patient is really well, and the lesion

Fig. 13.—Esophogram showing a traction diverticulum.

in his case was a simple ulcer; 3 are in good condition, the sputum containing no tubercle bacilli. All the others are suffering from active pulmonary tuberculosis, most of them being in a worse condition than when they were originally observed, and 3 have died.

There seem to be several reasons for the poor outcome. As has been previously mentioned, bronchial lesions are usually found in patients with rather far advanced pulmonary disease for whom the prognosis is poor. In more favorable cases, in which the condition is amenable to

collapse therapy, the beneficial effects of such therapy are negated by a persistent source of tuberculous sputum, with its potentialities for causing spread, located in a relatively inaccessible place and not affected by the artificial collapse. In a smaller group of cases in which the pulmonary disease has been arrested by natural or artificial means the patient may remain disabled because of the effect of stricture of the bronchus on the respiratory mechanism.

Treatment.—It is unfortunate that tuberculous disease of the bronchi is usually a complication of advanced, more or less hopeless disease of the lungs. For this reason it is often not possible to apply any form of treatment. It is important to keep in mind what one hopes to accomplish by the treatment of a tuberculous lesion in a bronchus. It has been repeatedly shown that simple tuberculous ulcers which involve the mucous membrane respond to cauterization with such chemicals as silver nitrate (case 1). It is even likely that in many cases such ulcerations heal spontaneously. In some cases it would appear that cauterization or the removal of granulation tissue which obstructs the bronchi is desirable.

With respect to tuberculous stricture of the bronchi, which is usually due to destruction of the wall of the bronchus, including the cartilage, and replacement with fibrous tissue, it is doubtful whether any form of endobronchial treatment is indicated or is feasible. Attempts to dilate strictures of this sort are practically always unsuccessful, as the narrowing of the bronchus is progressive and cannot be affected by mechanical means. The basis of this treatment is the belief that owing to the narrowing of a bronchus drainage from distal portions of the bronchial tree and of the lung is interfered with. Whether this is true or not, it would seem from our experience with the treatment of tuberculosis by collapse that bronchial drainage is much less important in the process of cure than physiologic rest of the lung. We have in some cases observed the partial occlusion of bronchi without any evidence of aggravation of the tuberculous process because of a failure of secretions to drain through them. On the contrary, in rare cases in which nature has succeeded in completely occluding a bronchus, the influence on the pulmonary lesion, even including cavities, has seemed, for a time at least, to be salutary. Unfortunately, tuberculous lesions of the bronchi, even when they produce extreme narrowing, practically always leave a small lumen through which tubercle bacilli may gain access to the general bronchial tree and thus infect other parts of the lung. If there is any merit in a procedure which could completely exclude a tuberculous lesion from the bronchial tree by complete occlusion of the bronchus, it would seem more logical to occlude than to dilate the stricture.

Unfortunately, it has not been possible, at least in human beings, to produce such a complete closure of a bronchus by means of escharotic agents.

SUMMARY AND CONCLUSIONS

By means of bronchoscopic and bronchographic study, confirmation of the diagnosis of tuberculosis of a major bronchus, clinically suspected, is possible.

Such lesions are more common than has been thought.

In most cases infection occurs by implantation of bacilli derived from peripheral pulmonary lesions; in a smaller number mediastinal lymph nodes may involve the bronchial wall.

The lesions are similar to tuberculous lesions elsewhere in the body; as a result of healing, fibrous strictures of the bronchi may occur; such strictures are rarely complete.

A simple ulceration or granuloma may be suspected when examination of the sputum continues to show tubercle bacilli after adequate collapse of cavities by natural or artificial means.

A wheeze and an accompanying rhonchus, when persistent, are symptoms of bronchial obstruction.

Objectively, atelectasis of a lobe or lobes is the outstanding manifestation; usually there is close correlation between the location of the involved lobe and that of the stenosed bronchus. Atelectasis of a lobe, unlike similar involvement of a whole lung, causes no appreciable mediastinal displacement. The onset of atelectasis of a lung during pneumothorax therapy is indicated by a fall (increased negativity) in intrapleural pressure.

Alterations in the mechanism of respiration may result.

Severe hemoptysis is occasionally the result of pressure of lymph nodes on the bronchus.

Cases of bronchial obstruction with no clinical evidence of pulmonary or glandular tuberculosis are reported; in such cases obstruction is due to perforation of the bronchial wall by anthracotic lymph nodes.

The general prognosis is poor, though not necessarily so.

Simple ulcerations may heal spontaneously or may be amenable to cauterization.

Dilation of strictures is deemed inadvisable.

A method of producing complete closure of the strictured bronchus would be desirable; this has not yet been achieved.

Drs. R. Kramer and M. Som performed the bronchoscopic studies. Drs. L. H. Siltzbach and M. J. Robin made the bronchograms. Drs. H. Neuhof and I. Kross furnished data and permitted us to report case 2. Dr. B. Stivelman gave us permission to reproduce figure 2*A* (case 4), and Dr. A. A. Epstein allowed us to report case 17.

OSCILLOMETRY IN DIAGNOSIS OF ARTERIOSCLEROSIS OF THE LOWER EXTREMITIES

A NEW METHOD OF APPLICATION

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The oscillometer is an instrument which measures in arbitrary units the amount of pulsation transmitted to a pneumatic cuff applied to a segment of an extremity. An excellent discussion of the history of oscillometry and of the nature and use of the available instruments, with bibliography, has been given by Samuels.[1]

Oscillometry has been advocated as a simple means of detecting decreases in arterial pulsation in peripheral arteriosclerotic disease. However, practical application of the science for this purpose by my associates and me proved disappointing, because the results obtained were often confusing. There is normally considerable variation in oscillometric readings recorded at the same level of an extremity in different persons. Thus at the supramalleolar level (the region just proximal to the ankle joint, corresponding approximately to the distal fourth of the leg), readings between 1 and 10 comprise the "normal" range. We, as will be shown, have recorded readings between 1 and 4 at this level in cases of peripheral arteriosclerotic disease. The confusion engendered is obvious. Our observation indicates that of two oscillometric readings of the same magnitude taken from different persons at a given level of an extremity one may indicate a normal and the other a grossly subnormal condition.

Variations in the size and tonus of the arterial trunks of the segment being tested—variations which, in turn, are related to the physical development of the limb and to its metabolic activity, respectively—are probably responsible for the fact that there is no standard normal oscillometric reading for any given level of an extremity. (Individual variations in the magnitude of the initial change in intra-aortic pressure, propagation of which constitutes the pulse, are also important in this regard.)

From the Peripheral Vascular Clinic of the Department of Surgery, Cleveland City Hospital, and the School of Medicine of Western Reserve University.

1. Samuels, S. S.: The Diagnosis and Treatment of Diseases of the Peripheral Arteries, New York, Oxford University Press, 1936.

In figure 1 two oscillometric tracings are shown. Each was taken at the left ankle of a young woman free of vascular disease. One tracing was taken early in the morning just before she started her day's work, the other at the end of the same day after a long period of work which involved considerable walking. The second tracing shows an increase in the amplitude of the pulse and illustrates the effect of increased metabolic activity on arterial pulsation.

Figure 2 shows a tracing taken at the left ankle of a fairly muscular young man. Comparison with figure 1 illustrates the difference in amplitude of pulse between these two persons, one robust, the other slender.

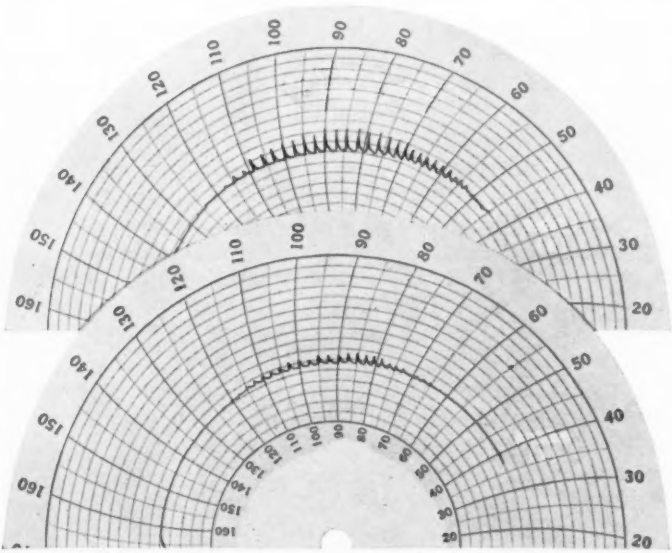

Fig. 1.—Oscillometric tracings taken at the left ankle of a young woman who is 22 years old, weighs 120 pounds (54.4 Kg.) and is free of vascular disease. The lower tracing was taken before and the upper tracing after a period of work involving considerable walking. Note the increase in the amplitude of the pulse. (The length of the longest spike is taken as the measurement of the amplitude.)

That corresponding differences in blood pressure do not necessarily accompany differences in oscillometric readings is illustrated by figure 3. Two tracings are shown, one taken from the left wrist, the other from the midbrachial region of the left arm. Although the systolic and the diastolic pressures are almost identical, the pulsation at the brachial level is greater.

Our problem, then, was to find some simple way of determining whether an oscillometric reading, irrespective of its absolute magnitude, represented a decrease in arterial pulsation, and if so, how great a decrease.

We started with the premise that since peripheral arteriosclerotic disease involves the lower extremities to a much greater extent than it

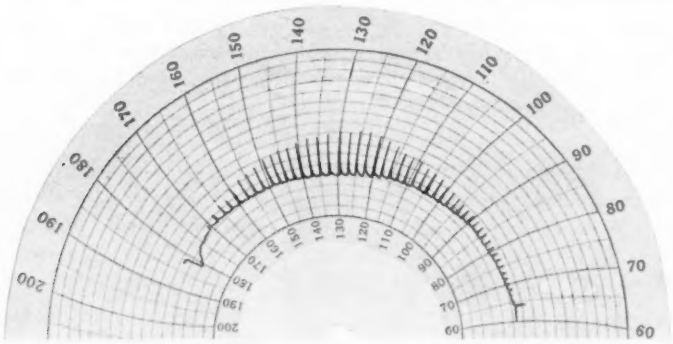

Fig. 2.—Oscillometric tracing taken at the left ankle of a fairly muscular young man 32 years old and weighing 167 pounds (75.7 Kg.). Compare this tracing with those in figure 1, and note the difference in amplitude of pulse.

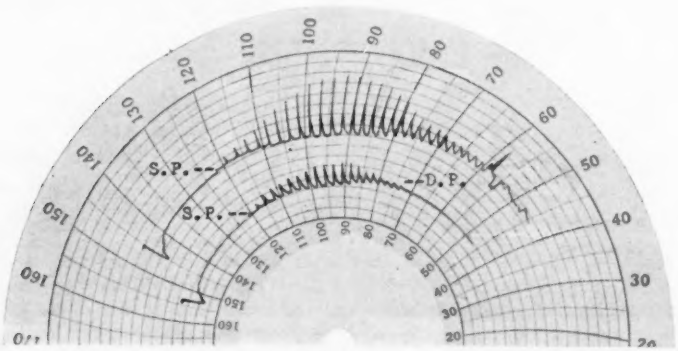

Fig. 3.—Oscillometric tracings illustrating the difference in amplitude of the pulse at different levels of an extremity, although the systolic (S. P.) and the diastolic (D. P.) pressures are almost identical. The lower tracing was taken at the left wrist of a young man 32 years old, the upper tracing at the midbrachial region of the same arm.

does the upper, oscillometric readings at any given level in the lower extremities should, as the disease progresses, decrease proportionately more than those at any given level in the upper extremities.

To test this hypothesis, we first took a series of oscillometric readings at the supramalleolar level and at the distal third of the corresponding forearm in active young adults free of vascular disease to establish the ratio that exists normally between oscillometric readings at these two levels. The supramalleolar region was chosen because arteriosclerotic disease of the lower extremity, with the exception of certain types of pain involving the calf, usually manifests itself distal to or at this level. Consequently, information revealing a decrease in arterial pulsation in this segment is particularly significant. In all the determinations the Boullitte oscillometer was used, the lower edge of the cuff being placed at the base of the internal malleolus and at the wrist joint.

In a series of 86 ratios thus obtained in which the reading at the supramalleolar level was used as the numerator, the lowest value was 1 and the highest 2, which means that in active adults free of vascular disease the magnitude of arterial pulsation in the lower part of the leg is at least equal to and may be greater than that in the lower part of the forearm.

Therefore, if the original premise is correct, that as peripheral arteriosclerotic disease progresses oscillometric readings at any given level in the lower extremities decrease proportionately more than those at any given level in the upper extremities, a point should be reached in the course of the disease at which the magnitude of arterial pulsation in the lower part of the leg becomes less than that in the lower part of the forearm and the ratio becomes less than 1. The corollary of this would be that a ratio less than 1, particularly when accompanied by other evidence of peripheral arteriosclerotic disease, should indicate decreased arterial pulsation in the lower leg; and the actual value of the ratio should be a rough measure of the extent of this decrease.

We therefore applied the ratio in examining a group of patients with arteriosclerotic disease of the lower extremities. This group had the following characteristics in common: All had disability sufficiently severe to have caused their referral to the clinic for persons with peripheral vascular diseases. All were ambulatory and active. In none could pulsations in either the dorsalis pedis or the posterior tibial arteries be felt.

The table presents a compilation of the 30 ratios obtained. All were well under 1, and in 16 instances the oscillometric readings at the supramalleolar level ranged between 1 and 4. An interesting observation is the wide variation in the values of the ratios. Some of the disparity may be due to a factor which we have no way of evaluating; that is, our inability to determine what the ratios were before the arteries became sclerotic. Obviously, to bring his ratio below 1 a person with an originally normal ratio of, say, 1.8 would have to have more severe arteriosclerosis in his lower extremities than a person with an originally normal ratio of 1.2. However, the aforementioned disparity is in line

with the observation we made clinically that the amount of disability suffered by a person with peripheral arteriosclerotic disease is not necessarily proportionate to the decrease in pulsation in the main arterial trunks. The larger vessels may not pulsate at all and still convey enough blood to meet the metabolic demands of the tissues.

Another qualifying factor to be kept in mind, particularly in basing a prognosis on the value of a ratio, is that the test gives information concerning arterial pulsation in the lower part of the leg only. While, as explained, this knowledge is pertinent, nevertheless, a ratio indicating

Ratio of the Oscillometric Reading at the Lower Part of the Leg to the Oscillometric Reading at the Lower Part of the Forearm in Thirty Cases of Arteriosclerotic Disease of the Lower Extremities

Type of Sclerosis	Oscillometric Readings: Lower Leg (Numerator)	Oscillometric Readings: Lower Forearm (Denominator)	Ratio
Senile	0.0	1.5	0.0
Senile	0.0	4.5	0.0
Senile	0.0	5.0	0.0
Diabetic	Trace	4.0	0.0
Diabetic	Trace	6.5	0.0
Senile	Trace	4.0	0.0
Senile	Trace	4.0	0.0
Senile	Trace	3.5	0.0
Senile	0.5	4.0	0.1
Senile	1.0	7.5	0.1
Senile	0.5	3.0	0.1
Diabetic	0.5	3.0	0.1
Senile	0.5	3.0	0.1
Diabetic	0.5	3.0	0.1
Senile	0.5	3.0	0.1
Senile	1.5	7.5	0.2
Senile	1.0	5.0	0.2
Senile	1.0	4.5	0.2
Senile	1.0	4.0	0.2
Senile	2.0	6.5	0.3
Diabetic	1.0	3.0	0.3
Senile	1.5	3.5	0.4
Senile	3.5	8.0	0.4
Senile	1.0	2.0	0.5
Senile	1.5	3.0	0.5
Senile	1.5	3.0	0.5
Diabetic	2.5	5.0	0.5
Senile	4.0	8.0	0.5
Senile	2.0	3.5	0.5
Diabetic	2.0	3.0	0.6

decreased but still relatively good pulsation in the lower part of the leg might be obtained and yet the patient might have an atheromatous plaque in the popliteal artery which could be the site of a sudden thrombosis, or the digital vessels to one or more toes might be relatively more diseased and suddenly thrombose, or the arteriolar bed might be sclerosed or in a state of spasm.

The practical utility of the test is that it enables the examiner to demonstrate in a roughly quantitative way decreased arterial pulsation in the lower part of the leg. When considered in conjunction with the history and with the results of the physical examination and of studies of the cutaneous temperature, the test assumes real significance.

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PERIARTERITIS NODOSA

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The relative rarity of periarteritis nodosa and the difficulty of recognizing its manifestations during life have brought it to the attention of numerous investigators. That the total number of cases reported is still comparatively small justifies our reporting 6 new cases occurring in recent years at the Peter Bent Brigham Hospital. Two additional cases have been reported previously from this clinic.[1] Thus, of 53,000 patients admitted for medical treatment to the Peter Bent Brigham Hospital since 1913, the diagnosis of periarteritis nodosa has been confirmed in the cases of only 8. It is to be hoped that increasing data may throw some light on the etiology of the disease and perhaps explain some of its bizarre symptomatology. We hope, too, that systematic recording of all the different syndromes that may result from the localization of the vascular process may help to increase the recognition of this disease during life.

REPORT OF CASES

CASE 1.—*A Chinese woman with a history of seasonal allergic rhinitis and clinical evidence of chronic glomerulonephritis, cirrhosis of the liver and healed pulmonary tuberculosis; death from uremia; widespread periarteritis nodosa revealed at autopsy.*

From the Renal Clinic and the Medical Service of the Peter Bent Brigham Hospital.

Assistance was received from the Fund for Research in Renal and Vascular Disease.

1. Bennett, G. A., and Levine, S. A.: Two Cases of Periarteritis Nodosa; One with Unusual Manifestations (Meningeal Form), Am. J. M. Sc. **177**:853 (June) 1929.

M. C., a 41 year old Chinese housewife, entered the hospital on Aug. 29, 1930, with complaints of jaundice and itching of the skin of three weeks' duration. The family history was noncontributory. The patient had had a fever, probably rheumatic, at the age of 19 and seasonal allergic rhinitis since the age of 30. A little over a year prior to entry she had suffered weakness and palpitation. A cough productive of a watery, frothy sputum had been present for over a year. Eight months before admission she vomited bright red blood on several occasions, and progressive loss of weight began. One month before entry shortness of breath, epigastric distress and backache were added to her symptoms. The abdominal pain was intermittent and localized in the epigastrium, with no radiation. About this time swelling of the ankles also appeared. One week later itching of the skin was noted, but obvious jaundice was not present until three days before the patient's admission. A week prior to admission she noted several bloody stools. Acholic stools had never been present. Nausea was present, but there was no recurrence of the vomiting.

Physical examination revealed a well developed but poorly nourished woman with obvious icterus of the skin and sclera. The pupils were slightly irregular, but equal; they were miotic and reacted sluggishly to light (? morphine). Ophthalmoscopic examination disclosed numerous fresh and old hemorrhages, particularly surrounding the maculas. There was dulness on percussion over the apexes of both lungs; elsewhere the note was resonant. Bronchial respiratory sounds were heard over the apexes and the interscapular region on the right. After coughing, fine, dry, subcrepitant rales were noted over these areas. On percussion, the heart was found to be enlarged, and the right border of dulness was noted to be 4 cm. to the right of the midsternal line. The apical impulse was felt at the anterior axillary line. A loud, rough systolic murmur was heard over the apex, and just below, a to and fro friction rub. There were no diastolic murmurs. The radial and brachial vessels were markedly thickened and tortuous. The blood pressure with the patient recumbent was 170 systolic and 108 diastolic. The abdomen showed generalized tenderness but no spasm or rigidity. The edge of the liver was not tender and was palpable 2 fingerbreadths below the right costal margin. The spleen was not palpable. The abdominal reflexes were not obtained. Peripheral edema was absent. Deep reflexes were present and active throughout, except for the ankle jerks. There were no sensory changes. No significant adenopathy was discovered. The temperature was normal on admission, but rose to 102 F. (rectal) within twelve hours and remained elevated during the rest of the patient's stay in the hospital. The pulse rate varied between 90 and 120 beats. Respirations were normal.

Of the laboratory data, the following were significant: erythrocyte count 2,500,000; hemoglobin 40 per cent (Sahli), and leukocyte count 23,300, with 87 per cent polymorphonuclears, 6 per cent lymphocytes, 6 per cent monocytes and 1 per cent basophils. No eosinophils were seen. Several urinalyses revealed specific gravities of 1.010 to 1.014, with a very slight to a slight trace of albumin, no sugar, and sediments containing rare red and white cells and 1 or 2 small granular casts per high power field. The stool gave a 3 plus reaction to the benzidine test, and stercobilin was present. The icterus index was 25 and the urea nitrogen of the blood 105 mg. per hundred cubic centimeters. Culture of the blood was sterile. The vomitus contained free hydrochloric acid. The Wassermann and Hinton reactions were negative.

The patient's course in the hospital was progressively downhill, and she died in coma on September 3, four days after admission. The clinical diagnosis was

the terminal stage of chronic glomerulonephritis, with pericarditis and uremia. The enlarged liver, the absence of any signs of cardiac decompensation and the jaundice suggested additional hepatic involvement, probably cirrhosis. Infestation with some obscure Oriental parasite was also advanced as a possible diagnosis. Old tuberculosis accounted for the findings in the apex of the chest. Thus to explain the bizarre picture at least three diagnoses had to be advanced.

The autopsy revealed pulmonary congestion and edema, cardiac hypertrophy and dilatation, serofibrinous pericarditis, fibrinous pleurisy on the left, generalized arteriosclerosis and arteritis with resultant tissue changes. Gross inspection showed that the hepatic, superior mesenteric, gastric, uterine and renal arteries were involved. The organs most affected were the liver and the kidneys. Many small, purplish, firm nodules were seen beneath the peritoneum, at the attachment of the mesentery to the small intestine. On cross section these nodules showed laminated, antemortem blood clots, which were adherent to the walls of their capsules. The capsules were continuous with the walls of the main arteries. It was interesting that no gross changes were noted in the peripheral, pulmonary or coronary vessels. Microscopic examination disclosed changes in the smaller pulmonary arteries and capillaries consistent with an early stage of acute arteritis. One thrombosed small artery was demonstrated in the spleen. There was evidence of chronic progressive vascular nephritis superimposed on thrombotic changes in the renal vessels. The vessels of the adrenals, urinary bladder, broad ligaments and uterus also were involved in the process. The changes were interpreted as characteristic of periarteritis nodosa.

CASE 2.—*A 19 year old Greek student with polyarthritis, unexplained low grade fever, leukocytosis, splenomegaly and cutaneous nodules; periarteritis nodosa shown by biopsy; clinical recovery of four years' duration.*

A. P., a 19 year old student, entered the hospital for the first time on Jan. 5, 1935, complaining of painful joints of five months' duration. The family history was entirely noncontributory. The patient's history was irrelevant. He had been free from symptoms until the onset of the recurrent attacks of articular pains which involved the extremities, starting in the "right foot." Two to three days after the onset the left ankle became involved. Within three weeks both ankles were swollen and painful. In rapid succession the wrists, elbows and fingers became swollen, painful and stiff. A series of intramuscular injections of typhoid vaccine had been given, without relief. Shortly thereafter he entered the hospital. He had lost 70 pounds (31.8 Kg.) in the preceding two and a half months.

Physical examination revealed a well developed but poorly nourished youth, apathetic but not acutely ill. Facial pallor was marked, and profuse sweating produced a peculiarly pungent odor. The fundi were entirely normal. The heart was not enlarged; the rhythm was regular, with a rate of 102; there were no thrills, rubs or murmurs. The blood pressure was 120 systolic and 80 diastolic. The liver and spleen were considerably enlarged. There was no peripheral edema. Several enlarged firm lymph nodes were found in the axillary and inguinal regions on both sides. There was diffuse tenderness over most of the muscles. The ankle joints were tender to palpation but were not swollen. The rectal temperature was 101 F.

The laboratory data revealed leukocytosis (18,400 cells), with 76 per cent polymorphonuclears, 23 per cent lymphocytes and 1 per cent eosinophils; the hemoglobin content was 60 per cent (Sahli), and the erythrocyte count, 4,900,000, with platelets approximately normal. Urinalyses showed concentrations of 1.005

to 1.023, with no albumin or sugar and with rare red cells but no casts in the sediment. The Wassermann and the Hinton reaction of the blood were negative. Because of the splenomegaly, anemia, arthritis and fever, diagnoses of undulant fever, rheumatic fever, chronic malaria and Felty's syndrome were first considered. Agglutination reactions with Bacillus melitensis were negative. Agglutination with the Bacillus typhosus group gave positive results in low titer, probably because of the previous injections of typhoid vaccine. Leukocyte counts varied from 6,000 to 18,000, but the erythrocyte counts remained rather constant. There was a daily elevation of temperature to 99 and 100 F. Salicylates were given, with no appreciable effect on the fever. Electrocardiograms revealed no prolongation of the PR interval. Roentgenograms of the sinuses and teeth showed no evidence of focal infection. Eleven intramuscular injections of typhoid vaccine were given, with good elevations of temperature and some alleviation of the articular symptoms. On February 25 a few small, tender, subcutaneous nodules, about the size of a pea, were felt on the flexor surface of the left forearm. With cessation of the injections of typhoid vaccine, the patient complained of the recurrence of articular pains. New crops of subcutaneous nodules appeared, with surrounding areas of induration about 2 cm. in size. These were considered to be lesions of erythema nodosum or the subcutaneous nodules of rheumatic fever. Unfortunately, a biopsy of one of the cutaneous lesions was not done. The patient was discharged on March 23.

He reentered the hospital on Oct. 28, 1935, with similar complaints of generalized weakness and intermittent pain and tenderness in the muscles and joints, especially those of the lower extremities. Against advice given him at the time of his discharge, he had been ambulatory during the interim. He had entered another hospital during the period, where the results of biopsy of one of the nodules had been reported as "suggestive of periarteritis nodosa." The clinical diagnosis, however, was uncertain when he was discharged from the hospital, against advice. In July he was seized by a vague, severe midabdominal "cramp," which was nonradiating in character but severe enough to double him up. There was no nausea, vomiting, constipation, diarrhea, dysuria, urinary frequency, jaundice or costovertebral pain. The pain disappeared spontaneously after several days. During the ten days prior to entry the patient had noted numerous erythematous, circinate lesions over the trunk and extremities. These were about 2 cm. in diameter and were elevated; they were not tender, but on palpation were found to be indurated. They appeared principally over the anterior and the posterior part of the thorax and the upper parts of the arms. Although weakness and sweating persisted, the patient had regained 25 (11.3 Kg.) of the 70 pounds (31.8 Kg.) he had lost.

Physical examination gave essentially the same results as on his previous admission. The temperature was 98.6 F.; the pulse rate was 96, and his blood pressure was 105 systolic and 65 diastolic. The edge of the liver was just palpable below the right costal margin. The firm, rounded edge of the spleen could be felt 4 fingerbreadths below the left costal margin. There was no lymphadenopathy.

The laboratory data revealed an erythrocyte count of 5,300,000 with 68 per cent hemoglobin (Sahli) and a leukocyte count of 9,800. There was 75 per cent polymorphonuclears and 25 per cent lymphocytes in the differential count. No eosinophils were found. The Wassermann and the Hinton reaction of the blood and the results of analyses of the stool and urine were again negative. Roentgenograms of the chest revealed only increased hilar shadows and pulmonary markings, compatible with chronic bronchitis. Biopsy of a subcutaneous nodule showed

two large arteries in which the lumens did not appear narrowed. There was evidence of intimal proliferation. The media was infiltrated with lymphocytes and mononuclears but showed little degeneration or fibrosis. The adventitia showed a marked reaction (fig. 1), with infiltration of lymphocytes, mononuclear cells and, rarely, plasma cells. A few polymorphonuclear leukocytes also were seen. A careful search for bacteria or inclusion bodies was without avail. There were no aneurysmal dilatations. There was no capsule about the nodule. The pathologic diagnosis was "periarteritis nodosa."

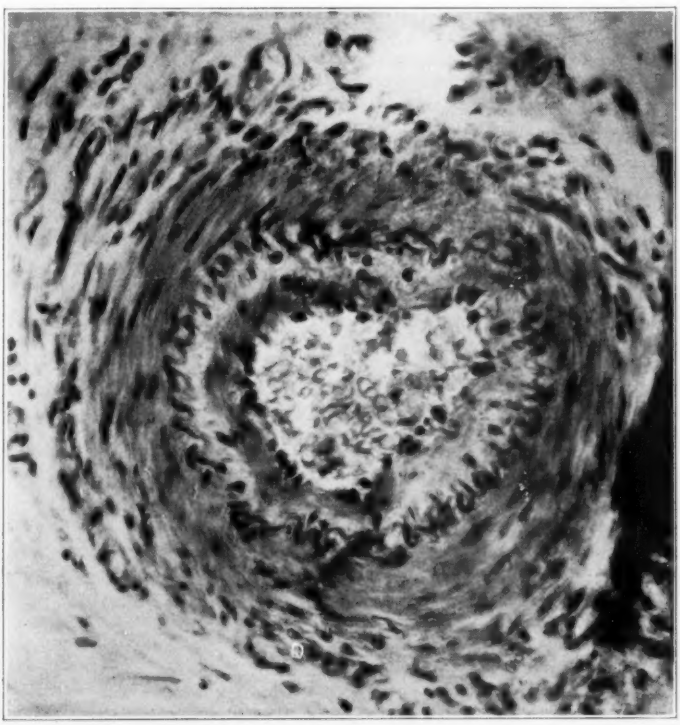

Fig. 1 (case 2).—A small artery from the subcutaneous tissue removed for biopsy. The intimal thickening is considerable. About the vessel are numerous lymphocytes and mononuclear cells. In other places these inflammatory cells were seen within the wall of the vessel (magnification, × 650).

After discharge from the hospital, the patient went to Florida, returning in April 1938. Examination disclosed no deviation from the normal, the liver and spleen no longer being palpable. There were no cutaneous lesions, and the blood pressure, the composition of the urine and the blood count were within normal limits. The patient had regained his lost weight and suffered no chills or fever. At present (August 1938) he is up and about and leads a normal existence.

CASE 3.—*A surgeon, presenting a vague picture of physical exhaustion, arthritis, fever, tachycardia, leukocytosis and rapidly appearing hypertension, with development of typical anginal attacks, peculiar neurologic findings and signs of glomerulonephritis; clinical diagnosis of periarteritis nodosa, confirmed by necropsy.*

T. E. C., a 56 year old surgeon, entered the hospital in September 1936, complaining of weakness, chills and fever of five weeks' duration. He complained also of arthritic pains, marked exhaustion and several attacks of irregular cardiac action. There were no other systemic complaints. His personal and his family history were irrelevant.

Physical examination revealed a pale, nervous, middle-aged man in a state of physical exhaustion. The skin was cold and clammy. Ophthalmoscopic examination gave normal results. Except for periods of paroxysmal auricular fibrillation, the heart appeared normal on auscultation, with no murmurs. There were a few moist rales over the base of the left lung. The abdominal examination gave normal results. There was no peripheral edema. The deep reflexes were active. There was marked hypesthesia over the lateral surfaces of both legs, with loss of the postural and the vibratory sense in the lower extremities. The blood pressure was 118 systolic and 80 diastolic. The two most significant signs were a low grade, intermittent fever, which continued throughout the patient's stay in the hospital, and leukocytosis (15,000 cells), with 95 per cent polymorphonuclears. There were no eosinophils. Urinalysis repeatedly gave normal results. The serologic reactions were negative. The spinal fluid was normal with no cells and normal dynamic readings. Chemical studies of the blood furnished no clue to the diagnosis. Agglutinations against B. typhosus, B. melitensis, Proteus X19 and the gonococcus gave negative results. Smears for malarial parasites were negative. Searches for hidden focal infection gave negative results. Cultures of the blood were sterile. The patient was finally allowed to leave the hospital for convalescence at home, no definite diagnosis having been made.

He reentered the hospital on November 30. In the interim he had been bedridden, and he now presented new complaints—tingling and numbness of the hands, as well as frequency and urgency of urination. Papilledema of the right nerve head and slight blurring of the left optic disk suggested the possibility of a brain tumor. Roentgenograms of the skull were considered to show no abnormality. The heart was now enlarged to the left, and there was a soft, blowing systolic murmur at the apex. The blood pressure was 120 systolic and 80 diastolic. The lungs were clear. Neurologic examination revealed atrophy of the intrinsic muscles of the hands, with ulnar, median and radial palsies. Cystoscopic examination, made because of difficulty in voiding, revealed only benign enlargement of the prostate. Roentgen studies of the gastrointestinal tract revealed nothing abnormal. Two observers thought the patient had periarteritis nodosa because a number of systems were involved. The intermittent fever continued, and the secondary anemia progressed. The patient was discharged from the hospital on December 5 and was followed at home. Typical anginal attacks soon developed, and later heart failure with pleural effusion required three thoracenteses. The fluid removed had the characteristics of a transudate. The blood pressure rapidly rose to 190 systolic and 110 diastolic, and though originally urinalyses had given normal results, subsequent ones revealed increasing amounts of albumin, red cells and hyaline casts. The urea nitrogen of the blood rose to 59 mg. per hundred cubic centimeters and the nonprotein nitrogen to 107 mg. Several weeks before the patient died a few nodules appeared in the skin of the left forearm, making the clinical diagnosis seem more certain. He died suddenly on March 8, 1937.

Autopsy disclosed that the immediate cause of death was bronchopneumonia. Gross examination disclosed two small aneurysmal dilatations of the mesenteric arteries, but histologic examination revealed lesions of periarteritis nodosa distributed widely. Those in the pericardium, peripheral nerves (fig. 2) and voluntary muscles were characteristic of the disease as usually described in the literature. The lesions in the peripheral nerves were acute. However, in the mesentery, the kidneys and elsewhere the lesions were apparently much older, with marked concentric thickening of the intima. The pathologist was uncertain whether the latter changes could be called healed lesions of periarteritis nodosa or atypical vascular lesions. Thus it was thought that in this case the various stages of the disease were well demonstrated.

The patient, who was considered by many to be psychoneurotic during the early course of his illness, presented marked loss of weight, chills and fever, paroxysmal

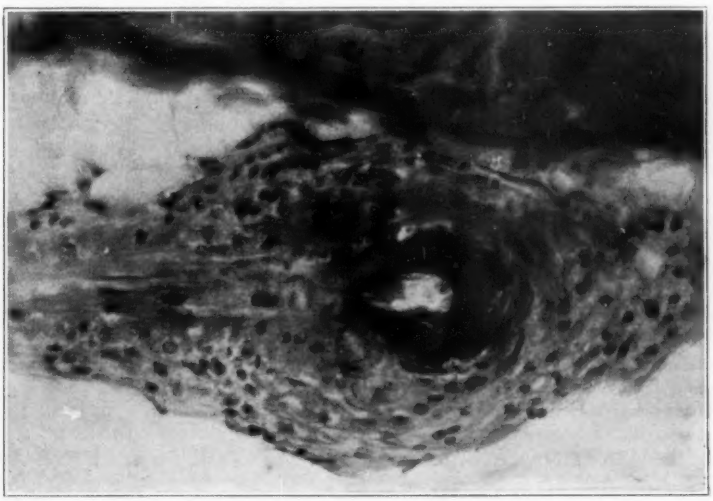

Fig. 2 (case 3).—A small arteriole adjacent to the sciatic nerve, the fibers of which are shown at the top of the illustration. Deep-staining necrotic material is present in the wall. All layers are heavily infiltrated with lymphocytes and mononuclear cells (magnification, × 490).

fibrillation, hydrothorax and peripheral neuritis. Signs and symptoms of nephritis, with hypertension and papilledema, as well as angina pectoris, later developed. A clinical diagnosis of periarteritis nodosa was made and confirmed by autopsy, which revealed that the condition involved vessels of the heart, gastrointestinal tract, mesentery, liver, kidneys, testes, peripheral nerves, voluntary muscles, spleen and prostate.

CASE 4.—*A woman with signs of hypertrophic arthritis, emphysema and chronic myocarditis; death from congestive heart failure with bronchopneumonia; widespread periarteritis nodosa revealed by autopsy.*

S. G., a 61 year old Russian housewife, entered the hospital on Dec. 30, 1936, complaining of pain in the shoulders and hips of one month's duration. Other than a slight productive cough of twenty years' duration, she could remember no previous symptoms. The pains in the shoulders and hips were described as sticking, knifelike, nonradiating and exaggerated by motion. There were no complaints of chills, fever or sweats, but the patient had noticed occasional palpitation over the heart, shortness of breath on exertion, malaise and weakness. For the two weeks preceding her entry progressive swelling of the ankles and orthopnea also were noted.

Physical examination revealed a small, emaciated, elderly woman in moderate respiratory distress with marked cyanosis. Examination of the head revealed no deviation from the normal. Numerous fine, sticky rales were heard over the bases of both lungs, but the percussion note was resonant throughout and whispered voice was normally transmitted. The heart was enlarged to the left. The heart sounds, although somewhat distant and rapid, were regular. No murmurs or rubs were heard. The blood pressure was 150 systolic and 100 diastolic. Abdominal examination did not disclose masses or tenderness. Abduction of the shoulders was markedly limited. Many of the small joints of the hands, the wrists and the left elbow were tender on palpation. There was moderate pitting of the ankle, with sacral edema. The temperature was 100 F. on admission and returned to normal after the fourth day in the hospital. The pulse rate was 104 and the respiratory rate 24. Urinalyses revealed concentrations of 1.030, with no albumin or sugar. The sediment contained occasional hyaline and several granular casts with no red or white blood cells. The hemoglobin content was 90 per cent (Sahli), the erythrocyte count 5,000,000 and the leukocyte count 12,800, with 71 per cent polymorphonuclears, 29 per cent lymphocytes and no eosinophils. The Wassermann and Hinton reactions of the blood were negative. Examinations of the stool revealed nothing abnormal. Despite supportive treatment, the patient became progressively weaker and died on the sixth day after entry.

No suspicion of periarteritis nodosa was entertained, the clinical diagnoses being bronchopneumonia, chronic myocarditis, hypertrophic arthritis, pulmonary emphysema, chronic bronchitis and generalized arteriosclerosis. Not until the microscopic sections were prepared was the underlying process determined.

Autopsy revealed bilateral bronchopneumonia with acute fibrinous pericarditis. Gross examination was not conclusive, but histologic examination of most of the organs, especially of the skeletal muscles, showed changes typical of periarteritis nodosa. The lungs, spleen, accessory spleen, pancreas, liver, kidneys, periadrenal tissue, uterus and skeletal muscles were involved.

CASE 5.—*A mill worker with fever, foot drop, wrist drop and signs of chronic glomerulonephritis; death from bronchopneumonia; periarteritis nodosa disclosed by autopsy.*

C. A. W., a 63 year old white mill foreman, entered the hospital on March 31, 1937, complaining of progressive weakness and loss of weight of one year's duration. His family history and personal history were noncontributory. Because of weakness he was forced to stop work in January. Two weeks later he entered a hospital, with edema of the ankles and palpitation. A letter from his local physician stated he had found "moderate emaciation, normal pupillary reaction, a small hemorrhage in the right retina, a grade 1 systolic murmur over the base of the heart, crackling rales at the bases of both lungs and a blood pressure of 120 systolic and 90 diastolic. The liver and spleen were not enlarged; the ankles

were slightly edematous; neurologic findings were normal except for a weak response of the quadriceps femoris muscle. Roentgen studies of the gastrointestinal tract revealed no abnormality. Lumbar puncture gave normal results except for absence of response to unilateral jugular compression, but a good rise in pressure followed bilateral compression." In the two weeks preceding entry the patient had become drowsy, markedly constipated and incontinent of urine and feces. Anorexia was marked. He had lost over 30 pounds (13.6 Kg.) in the preceding year.

Physical examination revealed a confused, delirious man without obvious respiratory embarrassment. There were spasmodic muscular twitchings and gross tremors of the arms and legs. The pulse was regular, with a rate of 120. The temperature was 101.3 F. and the respiratory rate 26 per minute. Heart sounds were distant, and no murmurs or rubs were heard. The blood pressure was 150 systolic and 90 diastolic. There was bilateral wrist and foot drop, but the deep reflexes were intact and there were no abnormalities of sensation. There was no peripheral edema.

Urinalysis showed 10 to 15 erythrocytes with a few hyaline and granular casts and no albumin or sugar. The hemoglobin content was 88 per cent (Sahli), the erythrocyte count 5,500,000 and the leukocyte count 17,600, with 92 per cent polymorphonuclears and no eosinophils. The serologic reactions were negative. The urea nitrogen of the blood was 30 mg. per hundred cubic centimeters and the total protein 5.3 Gm. per hundred cubic centimeters, with 2.2 Gm. of albumin and 3.1 Gm. of globulin. The spinal fluid was clear, with normal dynamic readings and laboratory findings. The clinical course in the hospital was progressively downhill, and death occurred on the third day in the hospital.

This case was another in which the patient presented a multiplicity of symptoms which could not be put in one category clinically and the typical arterial changes appeared only in the microscopic sections. The clinical diagnoses were chronic glomerulonephritis and polyneuritis on an avitaminotic basis. Lead poisoning also had been suggested.

Autopsy disclosed bronchopneumonia and several incidental gross changes. The nature of the underlying lesion was not evident until the microscopic sections were examined. These showed acute and extensive lesions of periarteritis nodosa included in the heart, gastrointestinal tract, pancreas, mesentery, gallbladder, kidneys, periadrenal tissue, urinary bladder, prostate, seminal vesicles and testes. The arterial lesions were associated with acute necrosis of the various organs.

CASE 6.—*A fireman with a verified gastric ulcer and macroscopic hematuria; death from uremia with pericarditis; widespread periarteritis nodosa and carcinoma of the stomach revealed by autopsy.*

J. M., a 64 year old fireman, entered the hospital on March 7, 1938, complaining of intermittent epigastric pain. His family history and personal history were noncontributory except that he had had sore joints from the age of 15. The soreness had not been severe enough to confine him to bed. There was no history of allergy. He admitted having taken five or six glasses of ale daily for years. He stated he was well until one year prior to entry. At that time he began to notice gnawing pain in the epigastrium, which radiated through to the back but not to either flank. The pain came on one to four hours after meals and at first was partially relieved by alkalis and food. Although mild at the onset, the pains sometimes doubled him up. About eight weeks prior to entry he visited his family physician and was placed on an "alkaline regimen" and liquid diet. This

gave no relief, and soon anorexia developed, with nausea at the sight of food. There were occasional vomitings of clear, watery phlegm. He did not suffer diarrhea, hematemesis or melena and had never noticed clay-colored stools or jaundice. For over a year he had noticed that his urine seemed "very red." On several occasions blood clots were passed, with no attendant dysuria. There was no history of retention of urine, incontinence, diminution in the force of the stream or pyuria. He had urinated once during the night for the preceding six months. The patient had never noticed any swelling of the ankles. He stated that he had lost about 15 pounds (6.8 Kg.) in the preceding four weeks.

Physical examination revealed an undernourished, wasted man, lying quietly in bed, somewhat drowsy but oriented. The temperature was 98.6 F., the pulse rate 76 and the respiratory rate 20 per minute. The breath was uriniferous. There was no pallor or cyanosis. Over the shoulders and back was an acneform eruption, and in both axillas were red macular patches. The tonsillar pillars, as well as the posterior part of the pharynx were beefy red. The heart appeared normal in size on percussion and presented no thrills or murmurs. The peripheral vessels were somewhat thickened, and the blood pressure was 155 systolic and 95 diastolic. The chest was hyperresonant, but auscultation revealed nothing abnormal. The abdomen exhibited voluntary muscular rigidity, most marked in the epigastrium. On palpation the edge of the liver was found to be firm, smooth and tender. No other organs were palpable. The deep reflexes were physiologic, but the Babinski phenomenon was present on the left. There was no peripheral edema. Ophthalmoscopic examination revealed only moderate arteriovenous nicking.

Laboratory findings included an erythrocyte count of 4,100,000, with 85 per cent hemoglobin (Sahli), and a leukocyte count of 14,000, with 85 per cent polymorphonuclears, 2 per cent eosinophils and 13 per cent lymphocytes. Urinalysis showed a concentration of 1.012, with a slight trace of albumin and sediment loaded with hyaline and fine brown granular casts; there were 3 to 5 red and 1 to 2 white blood cells per high power field. The excretion of phenolsulfonphthalein was 20 per cent. The urea nitrogen of the blood was 77 mg. per hundred cubic centimeters on admission and rose progressively to 136 mg. The icterus index was 6. The stool gave positive reactions to the benzidine test for blood. Analysis of specimens of vomitus showed 30 degrees of free hydrochloric acid. A series of examinations of the gastrointestinal tract revealed a constant, irregular filling defect involving the antral third of the stomach, with a crater 2 cm. in diameter along the lesser curvature. This was interpreted as a benign peptic ulcer. The rest of the tract was normal. Examination of the genitourinary tract revealed a sessile papilloma of the bladder about 3 cm. in diameter. This was not considered malignant, and fulguration was carried out through the cystoscope. Several days after admission a blotchy, red, maculopapular eruption appeared and became rapidly generalized, associated with moderate pruritus. When medication with barbiturates was discontinued, the rash only partially disappeared. After several days the temperature became as high as 103 F., dropping terminally. During the last forty-eight hours of his illness the patient exhibited marked restlessness, twitching and anuria. A loud pericardial friction rub was heard just before death, on the thirteenth day in the hospital.

Autopsy revealed multiple septic infarcts of the kidneys, hypertrophy of the heart with pericarditis, an area of ulceration on the lesser curvature of the stomach, which showed carcinomatous changes, and a benign papilloma of the bladder.

Microscopic examination showed disseminated periarteritis nodosa, involving the heart, spleen, stomach, jejunum, pancreas, liver, gallbladder, kidneys, ureters, urinary bladder, prostate, testes, adrenals and thyroid. Giemsa's and Levaditi's stains disclosed neither organisms nor spirochetes.

Thus, in a case in which the gastric and renal symptoms dominated the condition terminated in uremia with pericarditis. Clinical diagnoses were unsatisfactory in explaining all the symptoms presented. Autopsy revealed involvement of most of the organs of the body by the arterial lesions.

Analyzing these cases for frequency of symptoms and signs, one notes that fever was the only constant finding in the series. Loss of weight, weakness, edema, leukocytosis and hypertension occurred in 5 cases, and dyspnea, cough, abdominal pain, anemia, emaciation, albuminuria and hematuria appeared in 4 of the 6 cases. A summary of the other findings may be seen in table 1.

TABLE 1.—*Frequency of Symptoms and Signs in the Present Series of 6 Cases of Periarteritis Nodosa*

Disturbance	Frequency	Disturbance	Frequency
Fever	6	Arthritis	3
Loss of weight	5	Atrophy	2
Edema	5	Vomiting	2
Weakness	5	Cyanosis	2
Leukocytosis	5	Visual disturbance	2
Hypertension	5	Neuritis	2
Dyspnea	4	Nodules	2
Emaciation	4	Headache	1
Cough	4	Nausea	1
Abdominal pain	4	Convulsions	1
Albuminuria	4	Pain in the chest	1
Hematuria	4	Purpura	1
Anemia	4	History of allergy	1
Rapid onset	3	Vertigo	0
Icterus	3	Eosinophilia	0
Sensory involvement	3		

REVIEW OF THE LITERATURE

Credit is usually given to Kussmaul and Maier [2] for their description of periarteritis nodosa in 1866. However, it is of historical interest that Rokitansky [3] first described the macroscopic lesion in 1852, under the title "The Formation of Aneurysms of the Arteries in General, Except the Aorta and Most of Its Primary Branches, with the Further Exception of the Cerebral Arteries." Thirty-five years later Eppinger [4]

2. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteriitis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. **1**:484, 1866.

3. von Rokitansky, C.: Ueber einige der wichtigsten Erkrankungen der Arterien [table 6], Denkschr. d. k. Akad. d. Wissensch. **4**:49, 1852.

4. Eppinger, H.: Pathogenesis (Histogenesis und Aetiologie) der Aneurysmen einschliesslich des Aneurysma equi verminosum, Arch. f. klin. Chir. (supp.) **35**: 1, 1887.

reviewed the microscopic sections and confirmed the diagnosis. There is some reason for believing that the disease was recognized as early as 1755 by Michaelis and Matani [5] and again in 1810, by Pelletan,[6] who reported briefly a case in which he counted sixty-three small aneurysms of various arteries. It is of interest that Kussmaul and Maier first thought their patient had trichinosis.

Reviewing the world literature, one finds but 38 cases up to 1914, including 5 from the United States.[7] The first American reports were those of Dickson [8] in 1907 and Longcope [9] in 1908. In 1928 Strong [10] collected 21 cases from the journals published in English, and Curtis and Coffey [11] found but 38 cases up to and including 1933. Of these the diagnosis was made ante mortem in only 3. The total number of case reports that have reached the world literature up to June 1938 is slightly over 300, according to a check of the *Quarterly Cumulative Index Medicus* and the "Index-Catalogue of the Library of the Surgeon General's Office."

Reviewing the isolated case reports in the literature, we noted that since the survey of Gruber,[12] in 1926, no complete résumé of the literature, English or foreign, has appeared. The two surveys most often quoted are those of Strong (1928) [10] and of Curtis and Coffey (1934).[11] Strong tabulated the incidence of involvement of the major organs as well as the frequency of hypertension, asthma and arthritis in his 21 cases. Curtis and Coffey omitted the same data from their report of 17 collected cases, but added an analysis of most of the common symptoms and signs occurring in their series, to produce a much more comprehensive chart. Unfortunately, they did not tabulate all of the same data for the 21 cases previously collected by Strong. As a result, the combined chart gives one an erroneous impression of the frequency of the various symptoms and signs in the total series. Since the report

5. Michaelis and Matani (1755), cited by Eppinger [4] and by Schreiber, R.: Ueber Poliarteriitis nodosa, Inaug. Dissert., Königsberg, O. Kümmel, 1904.

6. Pelletan, P. J.: Clinique chirurgicale, ou mémoires et observations de chirurgie clinique, et sur d'autres objets, relatif à l'art de guérir, Paris, J. G. Denter, 1810, vol. 1.

7. Lamb, A. R.: Periarteritis Nodosa—A Clinical and Pathological Review of the Disease, with a Report of Two Cases, Arch. Int. Med. **14**:481 (Oct.) 1914.

8. Dickson, W. E. C.: Polyarteritis Acuta Nodosa and Periarteritis Nodosa, J. Path. & Bact. **12**:31, 1907.

9. Longcope, W. T.: Periarteritis Nodosa, with a Report of a Case with Autopsy, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **12**:60, 1908.

10. Strong, G. F.: Periarteritis Nodosa, with Report of a Case, Canad. M. A. J. **19**:534 (Nov.) 1928.

11. Curtis, A. C., and Coffey, R. M.: Periarteritis Nodosa: A Brief Review of the Literature and a Report of One Case, Ann. Int. Med. **7**:1345 (May) 1934.

12. Gruber, G. B.: Kasuistik und Kritik der Periarteriitis nodosa, Zentralbl. f. Herz- u. Gefässkr. **18**:198, 1926.

by Curtis and Coffey, in 1934, 57 more cases have been reported in the English literature up to June 1, 1938. If we were to add our 6 cases, the number of acceptable cases in the English literature would total 101. Fortunately, the case reports in the English literature, with 3 exceptions, have been outlined in great detail. On the other hand, many of the foreign reports were not acceptable for analysis, because of the lack of pathologic verification. Because of the various synonyms that have been applied to periarteritis nodosa by many pathologists, a search of the foreign literature has been unsatisfactory. Believing the 101 cases reported in the English literature to be a statistically significant number, we have restudied the entire series, tabulating (table 3) the frequency of the various symptoms, signs and laboratory findings as they appeared in the various case reports.[13] Realizing the bizarre forms the clinical picture of periarteritis nodosa might assume, we made it our basic purpose in assembling such a chart, now that a sufficient number of cases have been reported, to develop a composite picture of the condition. It was hoped that certain features would be more or less characteristic and that more frequent clinical recognition of the disease thus be allowed. The remainder of this report deals with our analysis and summary of the data compiled from the study of the 101 case reports.

ETIOLOGIC FACTORS

Various theories concerning the agent causing periarteritis nodosa have been presented. The suggestions include Spirochaeta pallida,[14] streptococcic infection,[15] virus infection[16] and parasitic invasion,[17] and

13. Thus, our chart resembles that of Curtis and Coffey closely in form but has additional columns for recording hypertension, arthritis and history of allergy, as well as for recording the involvement of the major organs noted at necropsy. We have omitted the nervous and cutaneous systems purposely, because of the exceedingly meager reports of their examination. For purposes of publication, it was necessary to report only the totals for the various data. These appear in tables 2 and 3. Throughout the remainder of this report we shall refer to these totals in terms of their frequency of appearance in the 101 original case reports, unless the reference is otherwise qualified.

14. (*a*) Kussmaul and Maier.[2] (*b*) Chvostek and Weichselbaum, A.: Herdweise syphilitische Endarteritis mit Aneurysmenbildung, Allg. Wien. med. Ztg. **22**:257, 1877. (*c*) Versé, M.: Periarteriitis nodosa und Arteriitis syphilitica cerebralis, Beitr. z. path. Anat. u. z. allg. Path. **40**:409, 1907.

15. Klotz, O.: Periarteritis Nodosa, J. M. Research **37**:1 (Sept.) 1917.

16. (*a*) von Haun, F.: Patho-histologische und experimentelle Untersuchungen über Periarteriitis nodosa, Virchows Arch. f. path. Anat. **227**:90, 1920. (*b*) Harris, W. H., and Friedrichs, A. V.: The Experimental Production of Periarteritis Nodosa in the Rabbit, with a Consideration of the Causal Excitant, J. Exper. Med. **36**:219 (Aug.) 1922.

17. Cameron, H., and Laidlaw, P. P.: Case of Periarteritis Nodosa, Guy's Hosp. Rep. **69**:159 1918.

recently an allergic reaction [18] has been postulated. The last theory is somewhat distinct from the earlier theories of hyperergy.[19] Suffice it to say that no conclusive evidence with confirmation has been brought forward to substantiate any of these theories. In only 1 of our cases, case 2, was any attempt made to recover or demonstrate the etiologic agent other than by routine antemortem and postmortem cultures of the blood. In this case the condition was recognized during life, and the patient's blood was injected into a guinea pig. Neither a febrile response nor any vascular lesions were subsequently noted. With such meager experimental data as that which we have obtained and that found in the literature, only the morphologic appearance of the tissue and the clinical course remain as a basis for speculations on the causation and nature of the process. The histologic appearance in several of our cases strongly suggested the type of reaction occurring in the vessels in the rickettsial diseases. Numerous attempts with appropriate stains, however, have failed to reveal Rickettsia bodies. No Aschoff bodies were seen in any of our cases. The clinical course was that of a generalized infectious process producing toxemia. The infrequency of pains in the joints and of further manifestations of arthritis in the 101 cases can only be emphasized. The relatively low frequency of a history of allergy, 15 per cent in the series, does not help us to place much faith in the theory of Cohen and others [18] that the lesions are the result of an irreversible allergic process involving the walls of the vessels. This theory suffers also from the fact that as yet no uniform histologic picture exists that would enable the pathologist to state that the lesion is allergic in nature. We are forced to conclude that no acceptable etiologic agent for periarteritis nodosa has yet been demonstrated.

PATHOLOGIC PICTURE

On the other hand, the pathologic character of periarteritis nodosa has been well established. According to Arkin,[20] one may divide the lesions into four stages: a degenerative stage, an acute inflammatory stage, a stage of granulation tissue and a so-called healed stage. Periarteritis nodosa involves the middle-sized arteries and arterioles. In the acute form the process has the appearance of an acute inflammatory reaction, involving one or all of the coats of the vessel. For the most part this reaction is distributed over segments of a vessel, the intervening

18. Cohen, M. B.; Kline, B. S., and Young, A. M.: The Clinical Diagnosis of Periarteritis Nodosa, J. A. M. A. **107**:1555 (Nov. 7) 1936.

19. Gruber, G. B.: Zur Frage der Periarteriitis nodosa, Virchows Arch. f. path. Anat. **258**:441, 1925.

20. Arkin, A.: A Clinical and Pathological Study of Periarteritis Nodosa. Am. J. Path. **6**:401 (July) 1930.

segments being spared, as emphasized by Kernohan and Woltman.[21] In many instances the reaction is confined to but one portion of the circumference of the vessel, but the wall may be involved completely. After the acute inflammatory reaction subsides, the polymorphonuclear leukocytes and scattered eosinophils are greatly outnumbered or entirely replaced by lymphocytes and monocytes, and at times by plasma cells. In the reparative stage the degree of fibroblastic proliferation varies, and on this variance apparently depends the formation of the small aneurysmal dilatations that are so conspicuous grossly in some instances. In other words, it is the lack of fibroblastic proliferation in such areas of weakness that allows for the dilatation and the formation of aneurysm. Where the intima is involved thrombi form (fig. 2), resulting in infarction of the area supplied by the involved vessel. These thrombi may form slowly, organize and become recanalized. If so-called healing occurs, there is marked cicatrization, resulting in thickening of the walls of the vessel and narrowing of the lumen. The appearance of

TABLE 2.—*Involvement of the Major Organs in 87 Cases of Periarteritis Nodosa in Which Autopsy Was Performed*

Organ	Frequency	Percentage
Kidneys	76	87
Heart	73	84
Liver	62	71
Spleen	27	31
Lungs	22	25

the lesions may vary in age and degree of involvement in different places in the same person, and in any given area one may see several stages of inflammation and repair blending together. The 87 cases in which autopsy was done collectively yielded examples of these changes, but all stages of the process were rarely shown in a single case.

Analyzing the involvement of the major organs, as noted in the 87 complete necropsies (table 2), we found that the organs in the order of their frequency of involvement were the kidneys, heart, liver, spleen and lung.

CLINICAL SYMPTOMS AND SIGNS

Inspection of table 3 discloses the following salient features in the 101 cases reviewed. Males outnumbered females in a ratio of approximately 3 to 1. The ages of the patients varied considerably, ranging from 6 to 71 years,[22] with an average of 36.9 years. In 58 cases the onset

21. Kernohan, J. W., and Woltman, H. W.: Periarteritis Nodosa: A Clinicopathologic Study with Special References to the Nervous System, Arch. Neurol. & Psychiat. **39**:655 (April) 1938.

22. Lamb[7] recounted a verified case from the European literature which involved a 2½ month old infant.

was rapid. The complete series shows an average duration of eight and six-tenths months from the beginning of symptoms until death. In the fatal cases, the longest durations were reported by Carr [23] (six years), Arkin [20] and Troutman [24] (four years).

The order of frequency of the more significant symptoms and signs was as follows: fever, leukocytosis (10,000 to 54,000 cells), albuminuria, rapid onset, abdominal pain, edema, loss of weight, hematuria and neuritis. In segregating groups of symptoms or signs as they might occur with vascular involvement of the various organs, we found that albuminuria occurred in 64 per cent of the cases and was associated with other signs of renal damage, such as hematuria and cylindruria, in 46 per cent of the cases. Hypertension occurred in 64 per cent of the cases in which a statement of the blood pressures was recorded. Abdominal pain occurred in 27 cases and was associated with icterus in 12 instances. Vomiting was noted in 31 cases; nausea, in 17 cases. Thoracic pain occurred in 36 instances and dyspnea in 41. Cyanosis was recorded in but 21 cases. Edema, however, usually of cardiac distribution, was commented on in 52 cases.

TABLE 3.—*Frequency of Symptoms and Signs in 101 Cases of Periarteritis Nodosa*

	Frequency		Frequency
Fever	80	Headache	29
Leukocytosis	70	Arthritis	27
Albuminuria	65	Atrophy	25
Rapid onset	58	Visual disturbances	23
Abdominal pain	57	Purpura	22
Edema	52	Cyanosis	21
Loss of weight	48	Eosinophilia	19
Neuritis	48	Nausea	17
Hematuria	47	Nodules	16
Hypertension*	46	Pain in the chest	16
Dyspnea	41	History of allergy	15
Weakness	41	Convulsions	15
Emaciation	36	Icterus	12
Cough	36	Vertigo	8
Vomiting	31	Positive serologic reaction	8
Sensory involvement	31		

* Since sphygmomanometric readings were not reported in the general literature before approximately 1915, we believe it justifiable to correct the percentage to 64 per cent.

With reference to cerebral manifestations, headache was present in 29 cases, vertigo in but 8 instances and convulsions in 15 cases. Visual disturbances were present in 23 cases. Peripheral manifestations were more frequent, neuritis appearing in 48 cases, involvement of sensory nerves in 31 instances and atrophy of various muscle groups, usually the intrinsic muscles of the hands or feet, in 25 cases. Cutaneous manifestations in the form of nodules appeared in only 16 cases. Purpuric

23. Carr, J. G.: Periarteritis Nodosa, M. Clin. North America **13**:1121 (March) 1934.

24. Troutman, W. B.: A Case of Periarteritis Nodosa with Autopsy Findings, Kentucky M. J. **29**:144 (March) 1931.

manifestations were present in 22 cases, and various other dermatoses appeared in individual cases.

General manifestations of toxemia or sepsis were represented in a high percentage of the cases. Fever was the most frequent sign, occurring in 79 cases. Weakness was noteworthy in 41 cases; emaciation, in 36. Leukocytosis appeared as the second most common finding, being present in 70 cases. Eosinophilia occurred in 19 cases. Anemia, although not recorded in table 2 because of the inexact methods of recording in the case reports, appeared in well over half the cases. Positive serologic reactions of the blood were found in only 8 cases. A history of allergy was obtained in 15 cases, and arthritis was specifically mentioned in 27 cases.

DIAGNOSIS

The report of Curtis and Coffey, in 1934, contained but 3 cases in which diagnosis was made ante mortem. To assist in making a correct antemortem diagnosis, many authors have attempted to coordinate the various diagnostic combinations of symptoms and signs that appear in the disease. For many years Meyer's [25] triad, "chlorotic marasmus, polymyositis and polyneuritis and gastrointestinal symptoms," later augmented by Brinkmann,[26] and Christeller's [27] fourth cardinal symptom complex, "nephritis," sufficed. Von Schrötter,[28] in 1899, implicated the "renal, abdominal, neuromuscular, cardiac and bronchial" systems. Harbitz,[29] in 1927, added the "cerebral and cutaneous" systems.

In the present series of 101 cases, diagnosis was made ante mortem in 26, including 2 of our own 6 cases. Most of these diagnoses were made by means of biopsy either of a cutaneous nodule or of a piece of muscle. Surgical specimens and laparotomy also afforded good opportunities for diagnosis. In several instances necropsy served to corroborate the suspected clinical diagnosis.

We believe, with Spiegel,[30] that "the syndrome is not complete without emphasis on the real clinical characteristic—a disproportion between the number and intensity of the symptoms and the disease which is assumed to be their cause." Thus it is in cases in which the diagnoses

25. Meyer, P. S.: Ueber Periarteriitis nodosa oder multiple Aneurysmen der mittleren und kleinen Arterienen, Virchows Arch. f. path. Anat. **74**:277, 1878.

26. Brinkmann: Zur Klinik der Periarteriitis nodosa, München. med. Wchnschr. **69**:703 (May 12) 1922.

27. Christeller, E.: Ueber die Localisationen der Periarteriitis nodosa, besonders in den Bauchorganen, Arch. f. Verdauungskr. **37**:249, 1926.

28. von Schrötter, L.: Ueber Periarteriitis nodosa, Wien. klin. Wchnschr. **12**: 404, 1899.

29. Harbitz, F.: Different Forms of Arteritis, Especially Periarteritis Nodosa, Internat. Clin. **1**:130 (March) 1927.

30. Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**:993 (Dec.) 1936.

that are advanced generally seem to be poorly supported and do not satisfactorily explain all the manifestations that the diagnosis of periarteritis nodosa must be most seriously considered.

PROGNOSIS

Of the 101 patients, 10 were reported as "recovered" [31] at the time the case was described. We have communicated with each author who reported a case with recovery and have received replies from all but one. No follow-up information could be obtained in 3 cases. In the 6 remaining cases, 1 patient had died of what was apparently a coronary lesion, and the other 5 are alive at the time of this writing. Thus, 9 of the 10 patients may still be alive. Although these revised statistics indicate that the former prognosis of "100 per cent fatal" is incorrect, they show that cases in which there is recovery or long survival are exceptional.

TREATMENT

Unfortunately, recovery in the reported cases did not follow any known therapy. S. pallida has long been discredited as the possible etiologic agent. Nevertheless, each succeeding report on periarteritis nodosa almost invariably has mentioned the 2 cases in the literature in which arsphenamine therapy was employed, that reported by Schottstaedt and that by Carling and Hicks. Neither of the patients had a positive serologic reaction. Despite many statements in the literature to the contrary, Carling and Hicks used arsphenamine merely as a provocative test in attempting to reverse the negative serologic reaction of their patient. This procedure failed, however. We can conclude only that no treatment for periarteritis nodosa, other than symptomatic, can be recommended at present.

COMMENT

From the analysis of the data in our charts, as summarized in tables 2 and 3, certain conclusions seem to be justified. Periarteritis nodosa is seen more frequently in males than in females. It occurs chiefly in adult life, but in no special decade. In slightly more than

31. (*a*) Carling, E. R., and Hicks, J. A. B.: A Case of Periarteritis Nodosa Accidentally Recognized During Life, Lancet **1**:1001 (May 19) 1923. (*b*) Schottstaedt, W. E. R.: Periarteritis Nodosa with Remission of Symptoms, California & West. Med. **36**:186 (March) 1932. (*c*) Motley, L.: Periarteritis Nodosa, with Report of Case Showing Unusual Features and Apparent Recovery, J. A. M. A. **106**:898 (March 14) 1936. (*d*) King, E. F.: Ocular Involvement in a Case of Periarteritis Nodosa, Tr. Ophth. Soc. U. Kingdom **55**:246, 1935. (*e*) Bernstein, A.: Periarteritis Nodosa Without Peripheral Nodules Diagnosed Antemortem, Am. J. M. Sc. **190**:317 (Sept.) 1935. (*f*) Cohen, Kline and Young.[18] (*g*) Spiegel.[30] (*h*) Our case 2.

one-half the cases the onset is rapid. The duration of the disease usually is a matter of months, although Macaigne and Nicaud [32] described a case in which the illness lasted for twelve years. The patient in case 2 in our series is now entering his fourth year since the onset of symptoms. In the last two years he has been entirely asymptomatic. An examination just prior to the writing of this report disclosed a recent gain of weight, a normal blood pressure, normal urine and no essential physical deviation from the normal. The absence of abnormal urinary findings at any time offers itself as an explanation for the continued well-being, for we have been struck repeatedly by the sharp downhill course that the patients pursue once renal impairment has set in.

As already noted, our analysis did not yield any truly characteristic or diagnostic symptoms or signs. The most frequent findings—fever, leukocytosis, albuminuria, abdominal pain, edema, loss of weight and hypertension—do not represent a clear diagnostic picture. Bernstein [31e] has called attention to the fluctuations in the blood pressures, but we believe that the rapid rise to high levels, as in our case 3, is of greater importance. Such rapid rises are frequently associated with other signs of renal involvement and, as we have pointed out, are especially significant of a relatively rapid fatal termination. The order of frequency of the other symptoms, signs and abnormal laboratory findings agree in the main with those cited by other observers. The frequency of abdominal pain is noteworthy. It may be associated not only with infarcts involving the various abdominal viscera but also with coronary thrombosis and actual perforations of the viscera. The distress in the upper part of the abdomen usually associated with the chronic passive congestion of heart failure is also not uncommon.

In contrast to the frequency of abdominal pain, thoracic pain is relatively rare. This fact is surprising in the face of the frequency of cardiac involvement noted at necropsy. The type of thoracic pain usually reported was typical of angina pectoris. The literature states that pulmonary involvement is rare. Actually, this statement is exaggerated, for reference to table 2 discloses that, although of the five organs summarized the lung was involved least frequently, it was affected in one fourth of the 87 cases in which autopsy was done. The frequent occurrence of cough and dyspnea therefore is not surprising. However, the frequency of cardiac involvement and heart failure was probably the actual cause of the frequent occurrence of cough and dyspnea in the series. Nevertheless, both appeared less frequently than edema, which usually was of cardiac distribution.

32. Macaigne, M., and Nicaud, P.: Périartérite noueuse (maladie de Kussmaul) à form chronique, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:665 (April 21) 1930.

Eosinophilia and nodules in the skin have long been recognized as of diagnostic aid, but, unfortunately, their frequency is not great. Eosinophilia occurred in but 19 instances and nodules in but 16. These recordings are somewhat higher than those given by Gruber.[12] The replacement of the eosinophilia by a marked shift to the left, with a high percentage of polymorphonuclears, coincident with the occurrence of a complication, usually abdominal, is noteworthy and puzzling to the observer. It should serve to raise the question of periarteritis nodosa. In addition to nodules, many other types of cutaneous lesions have been described, chief among which are purpuric rashes, usually macular in type. Urticarial lesions are encountered infrequently.

Several authors[10] have called attention to the frequent finding of splenomegaly. In our analysis (table 2), we were unable to confirm this either in the antemortem accounts or in the postmortem observations. In fact, the spleen is one of the least involved of the major organs, the actual frequency of involvement being 31 per cent, which is but slightly greater than that of the lung by the vascular process. This fact is somewhat against an infectious bacterial agent as the etiologic factor in the disease. Although the incidence of involvement of the liver was rather high, 71 per cent, icterus was mentioned in but 12 of the 101 cases. The explanation may lie either in the failure of many authors to recognize minor degrees of icterus or in its absence during the time of observation though it may have been present at one time during the course of the illness. It is noteworthy that Pass,[33] in a review of the cases of hepatic infarcts in the literature, found periarteritis nodosa to be the most frequent cause of such lesions. In fact, Arkin[20] has said that hepatic and renal infarcts in the absence of endocarditis should make one think of periarteritis nodosa as the cause.

SUMMARY

Six additional cases of proven periarteritis nodosa are reported. In 2 of them diagnosis was made ante mortem.

All the cases of periarteritis nodosa reported in the English literature prior to June 1, 1938—101 cases—were studied and the frequency of symptoms, signs and abnormal laboratory findings tabulated. Totals for these are presented.

The data thus assembled do not afford an answer to the question of causation. They do not substantiate the proposed allergic theory.

Although there were 26 antemortem diagnoses in the 101 case reported, an analysis of the clinical symptoms and signs did not reveal a characteristic clinical pattern.

Dr. G. Darrell Ayer prepared the photomicrographs and assisted in analyzing the necropsy material.

33. Pass, I. J.: Infarction of the Liver, Am. J. Path. **11**:503 (May) 1935.

ROENTGEN DIAGNOSIS OF MURAL THROMBI

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NEW YORK

Considerable interest has been aroused in the last few years regarding the roentgen diagnosis of mural thrombi. Yet, in reviewing the literature on this subject, I find that few mural thrombi have been roentgenologically recognized during life and the diagnosis confirmed by necropsy.

From my own experience and that of other observers it is apparent that calcified mural thrombi usually occur in mitral stenosis and are commonly situated in the left auricle. Only 5 cases of mural thrombosis have been reported in the literature. These consist of 3 cases of calcified mural thrombi reported by Scholz,[1] Besser and Schilling [2] and Heeren [3] and 2 cases of noncalcified mural thrombi reported by Arendt [4] and Fussl.[5]

Prompted by this situation, I wish to report a case of calcified mural thrombus in which the condition was recognized during life and the diagnosis confirmed by necropsy.

Roentgenoscopic and aimed roentgenographic technics are important factors in recognizing mural thrombi. One should search for the lesions carefully, with the eyes well adapted under the roentgenoscope and with the smallest diaphragm. Preferably the patient should be placed in the right oblique position. Calcified mural thrombi are round or semilunar. They are rather dense and sharply outlined. Larger than valvular calcifications, they have a dancing motion which is synchronous with the heart beat.

Noncalcified mural thrombi may be recognized by variation in the contour of the normal cardiac silhouette. Lying within the cardiac

From the First Medical Division of the Bellevue Hospital, Dr. I. O. Woodruff, Director, and the Department of Laboratories, Dr. D. Symmers, Director.

1. Scholz, T.: Röntgenologische Darstellung von Herzthromben, Fortschr. a. d. Geb. d. Röntgenstrahlen **32**:416, 1924.

2. Besser, P., and Schilling, C.: Zur Klinik und Röntgenologie der Herzthromben, Deutsches Arch. f. klin. Med. **175**:50, 1933.

3. Heeren, J.: Zur Röntgendiagnose verkalkter Herzthromben, Fortschr. a. d. Geb. d. Röntgenstrahlen **50**:490, 1934.

4. Arendt, J.: Röntgendiagnose Herzthromben, Röntgenpraxis **2**:828, 1930.

5. Fussl, E.: Beitrag zur Röntgendiagnose, der nichtverkalkten Herzthromben, Röntgenpraxis **8**:377, 1936.

shadow, the thrombus may be seen as a denser shadow which moves only slightly during systole. Because of its similarity to the cardiac shadow, however, it is seldom recognized. In some cases one can definitely recognize a noncalcified mural thrombus only if it becomes so large that it causes a marked change in the normal cardiac configuration.

REPORT OF A CASE

V. M., a 56 year old married Italian woman, was admitted to the Bellevue Hospital on Jan. 14, 1938, suffering from dyspnea and edema of the ankles. She had been admitted to several hospitals for varying periods because of dyspnea, edema or palpitation, and apparently remaining until improvement occurred, after which she was discharged to continue invalidism at home.

Physical examination revealed an undernourished, emaciated woman who was cyanotic, dyspneic and orthopneic. Malar flush was present, and the temporal veins were dilated. The veins of the neck were distended and pulsating. The lungs revealed moist rales at both bases. The heart was greatly enlarged to right and left, with the point of maximal impulse in the anterior axillary line. There was a systolic thrill at the apex, with a rough systolic blow, a diastolic rumble and a blowing systolic murmur at the base. There was no aortic diastolic murmur. The aortic second sound was faintly heard over the vessels of the neck. The pulmonic second sound was accentuated. There was rapid auricular fibrillation. The liver was large and tender and was located 4 fingerbreadths below the costal margin. There was edema of the sacrum and of the lower extremities up to the midthigh. During her stay in the hospital the patient received digitalis, ammonium chloride and mercupurin (a mercurin-theophylline preparation); oxygen was administered nasally, and thoracentesis was repeatedly performed on the right. The course was progressively downward, with congestive heart failure. The patient died on May 2.

Laboratory Data.—The electrocardiogram revealed auricular fibrillation. There was left ventricular preponderance. The T waves in leads I and II were inverted, showing the effect of digitalis. The Wassermann reaction was negative. The hemoglobin content of the blood was 72 per cent. The erythrocyte count was 4,310,000.

Roentgen Examination.—The thorax was asymmetric, owing to scoliokyphosis of the dorsal part of the spine. The heart was markedly enlarged to the right and left; the right median diameter was 8.4 cm. and the left median diameter 9.8 cm.; the transverse diameter of the heart was 18.2 cm.; the diameter of the chest was 21.2 cm. (fig. 1).

The heart was of mitral configuration; the left ventricular arch was intensified and the apex rounded and elevated. The right cardiac border was irregular, with multiple irregular calcifications, which were localized in the lateral view as linear calcified shadows. The posterior and lower cardiac border revealed pleural adhesions to the right side of the diaphragm.

Fluoroscopic examination revealed a calcified semicircular ring just to the left of the midplane, showing a dancing motion toward the apex suggestive of calcification of the mitral valve (fig. 2). Another oval calcified ring, which appeared to be smooth, was seen in the posteroanterior position. By rotating the patient in the right oblique position the semicircular, sharply outlined and intensified shadow could not be projected outside the cardiac silhouette and appeared to lie within the left auricle. In the left oblique view the dense, semicircular shadow was at the same level; yet it lay about 0.5 cm. from the cardiac border and was clearly

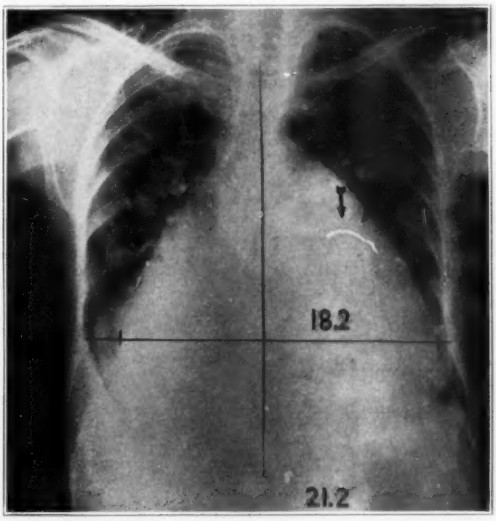

Fig. 1.—Posteroanterior view of a markedly enlarged heart, with a dense shadow of calcification of the mitral valve.

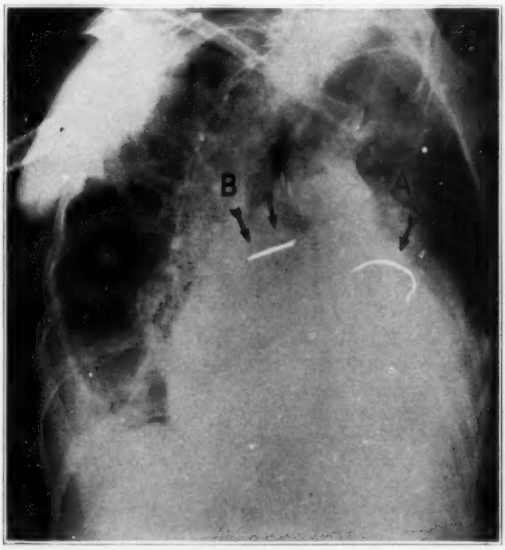

Fig. 2.—Right anterior oblique view of the heart. *A*, calcification of the mitral valve. *B*, dense calcification of the left auricle.

visible within the cardiac silhouette (fig. 3). Beneath these were seen irregular, linear, segmented calcium shadows showing only minimal pulsation. When the patient was rotated these were seen running parallel to the cardiac border, suggesting pericardial calcification (fig. 4).

Necropsy.—The heart weighed 450 Gm. The pericardium was calcified posteriorly over an area about 7 cm. in diameter. The heart lay free in the pericardial sac, which contained 200 cc. of clear yellowish fluid. The epicardium was smooth and of normal transparency. The right auricle was dilated to about twice its normal size. The fossa ovalis was closed; the endocardium was normal, and the right auricular appendage was free of thrombi. The tricuspid ring admitted three fingers. The valve cusps showed thickened edges, with no visible verrucae. The valve appeared competent; the chordae tendineae were thickened, shortened and

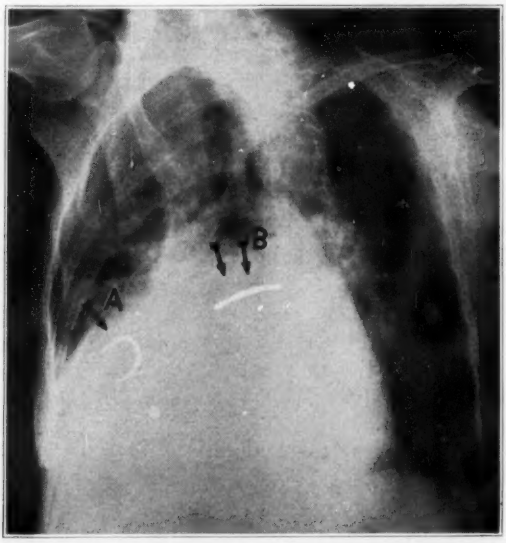

Fig. 3.—Left oblique view of the heart. *A*, semicircular calcification of the mitral valve. *B*, dense calcification of the left auricle.

fused. The papillary muscles were hypertrophied, as were the trabeculae carneae and the myocardium of the dilated right ventricle. The muscle wall measured 3 to 10 mm. in thickness. The endocardium of this chamber was normal. The pulmonic valve was normal. The pulmonary arteries showed many soft atherosclerotic plaques. The left auricle presented a bizarre aspect. It was dilated to two or three times the normal size. Most of the endocardial surface was covered with adherent, friable, crumbling thrombotic material, which completely filled and distended the auricular appendage. This had undergone organization and calcification, so that the appendage projected perpendicularly from the auricle as a bony nodule. The cusps of the mitral valve were so thickened and fused that the opening was narrowed to a fish-mouth-like slit of 5 to 10 mm. The leaflets were stiff with calcific deposits (fig. 5). The chordae tendineae were so shortened

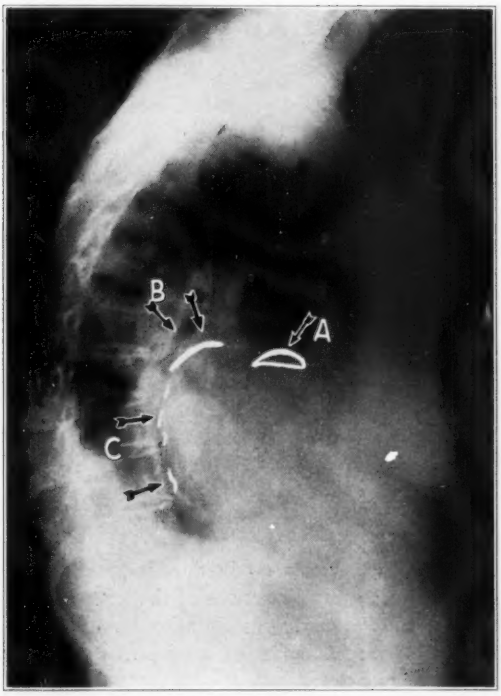

Fig. 4.—Lateral view of the heart. *A*, fish-mouth-like slit of the calcified mitral valve. *B*, linear calcified shadow of the left auricle. *C*, irregular pericardial calcification running parallel to the cardiac border.

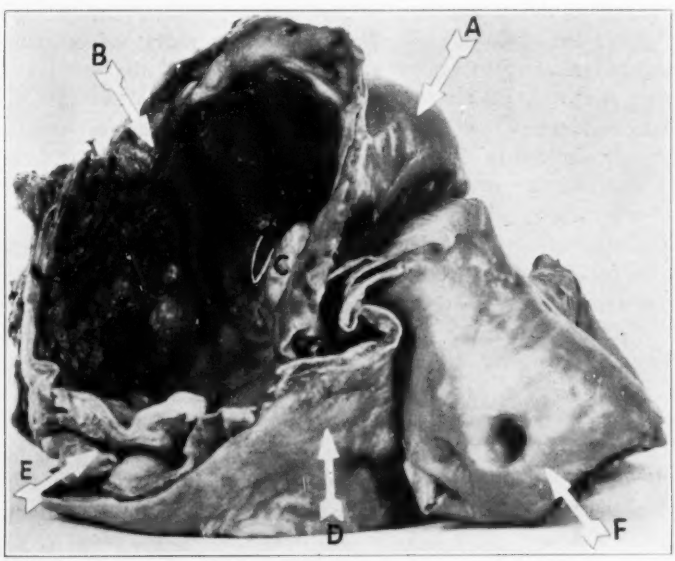

Fig. 5.—Autopsy specimen, with opening into the left auricle. *A*, calcified appendage of the left auricle; *B*, mural thrombus of the left auricle; *C*, fish-mouth-like slit of the calcified mitral valve (unopened); *D*, right auricle; *E*, right ventricle, and *F*, aorta.

that the cusps were practically attached to the papillary muscles. The greatly thickened and fused chordae could not be clearly differentiated from the thickened edges of the valve cusps. The left ventricle was of normal size; its endocardium and myocardium appeared normal. The latter measured 1 to 1.5 cm. in thickness. The aortic ring was normal in size, with no thickening of the valve cusps. The coronary arteries had normal ostiums, showing slight thickening of the walls in places, but no yellowish atheromatous or calcified plaques were present. The aorta was small and elastic; the intima showed a few atheromatous plaques, none of which were calcified or ulcerated.

The spleen weighed 150 Gm. The capsule was not thickened. The parenchyma revealed a firm, fibrous pulp; the malpighian bodies were not discernible. The capsule of the liver was of normal transparency and was smooth except over the diaphragmatic surface, where there were fibrous adhesions. The cut surface revealed a marked distortion of the normal architectural markings and apparent contraction of the lobules, with some replacement by fibrous tissue.

COMMENT

This case is of particular interest because it presents three types of intracardial calcification: mural thrombus of the left auricle, calcification of the mitral valve and pericardial calcification. Although difficult, the differential diagnosis can be made with modern roentgenoscopic and roentgenographic technic.

Calcified valves are situated more medially than calcified coronary arteries. The calcified mitral valves are seen more to the left of the spine in the direct posteroanterior view and near the posterior cardiac wall in the left antero-oblique view. The aortic valves are located low at the left border of the spine in the former view and about in the middle in the latter view. They are usually semilunar, the mitral valve showing a marked pulsatory movement toward the apex and the aortic valve showing a dancing motion.

Calcified mural thrombi usually occur in mitral stenosis and are commonly situated in the left auricle. They are round or semilunar, dense and sharply outlined. They are larger than the valvular calcifications and show a dancing motion.

Calcified cardiac aneurysms appear semilunar and large, with a strong systolic pulsation. Their site of predilection is near the apex. Pericardial calcifications are more frequently located on the lower surface of the right ventricle but also occur in the coronary sulcus, usually leaving the apex free. They are solid, linear and often branching and have only a minimal pulsation. On rotation of the patient they can be seen to run parallel to the cardiac border.

Calcified costal cartilages are denser and more clearcut, and one may identify them by following their course. Calcified glands and calcifications in the lungs and mediastina are round and dense. By rotation of

the patient these can be projected outside the cardiac shadow. They move upward and downward with respiration. The bronchi can be easily differentiated.

SUMMARY

A case of calcified mural thrombus of the left auricle is presented with the purpose of demonstrating the great diagnostic value of roentgenoscopic and roentgenographic technic. In this case there were three types of intracardiac calcification: calcification of the mitral valve, pericardial calcification and mural thrombus of the left auricle. These were clearly differentiated in vivo and confirmed by necropsy.

As roentgenoscopic and roentgenographic technic improves, an ever growing number of cases of mural thrombus of the left auricle will be recognized. However, the successful roentgenologic diagnosis will be made more frequently than it has been in the past only if one is vigilant and constantly aware of the possible existence of such a lesion.

Progress in Internal Medicine

BLOOD

A REVIEW OF THE RECENT LITERATURE

CYRUS C. STURGIS, M.D.

RAPHAEL ISAACS, M.D.

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The present review includes articles on phases of hematology published in 1938 and a few articles that appeared in 1937 but were not included in the last review. Because of the increasing number of publications it has been necessary to select certain articles, somewhat arbitrarily at times, and some important contributions no doubt have been omitted. These may be included in forthcoming reviews of articles on diseases of the blood. The trend of hematology appears to be toward the increased reference to the state of the bone marrow in various conditions, especially observations derived from material obtained on sternal puncture, the increased use of quantitative data, the establishment of data for "normal" conditions and the chemical physiology and pathology of disease.

PERNICIOUS ANEMIA

Askanazy [1] has gathered statistics as to the distribution of pernicious anemia in various parts of the world. The incidence varied from no cases in twenty years in Java to 9.1 in Canada and 9.18 per hundred thousand in Sweden. The incidence for the United States is given as 6.9. The percentage shown for autopsy studies varied from 0.04 in Tübingen, Germany, to 1.39 in Warsaw. Data as to various body lengths, weights, state of nourishment and weights of the bone marrow, spleen and liver have been given. The incidence of funicular myelosis varied from 4.7 per cent in a series studied in Munich to 60 per cent in a series studied in Toronto. Data for constitutional hemolytic anemia, constitutional achylic anemia and secondary anemias and leukemias have been given.

1. Askanazy, M.: Die pathologische Anatomie der Anämien, in Comptes rendus de la troisième Conférence internationale de pathologie géographique, Helsingfors, Mercators Tryckeri, 1937, p. 32.

The present status of knowledge relating to nutritional deficiencies and the macrocytic anemias was considered in the Goulstonian Lecture delivered by Ungley [2] before the Royal College of Physicians on March 8, 1938. His own experiments confirmed Meulengracht's observation that the pepsin and the antianemic factor are disassociated physiologically and anatomically in the stomach of the swine. For example, the mucosa of the fundus contains pepsinogen but no intrinsic factor, whereas the mucosa of the pylorus does not contain appreciable amounts of pepsin or pepsinogen but is a good source of the intrinsic factor. In view of these observations, it is interesting to note that Magnus and Ungley [3] observed that the stomachs of 7 patients with pernicious anemia at necropsy showed profound atrophy involving all the coats of the wall and localized to the body of the organ. The pyloric antrum and duodenum, where it had been assumed that the intrinsic factor of Castle was produced, showed no pathologic abnormality. These findings therefore provide an anatomic basis for the achylia gastrica but not for the absence of the intrinsic factor, if it is assumed that it is produced in the regions mentioned. According to these authors, the same unexpected findings were observed by Meulengracht, who transmitted this information to them in a personal communication. From a study of their material, they concluded that the gastric lesion in pernicious anemia is almost certainly not the end result of inflammatory gastritis. It is to be regarded as more of the nature of an atrophic process the cause of which is unknown but which may be the end result of some endocrine or nutritional deficiency or perhaps may even be of congenital origin. They concluded that probably regeneration to normal gastric mucosa never occurs. This statement may be correct, but one wonders if regeneration is any more unlikely in the gastric mucosa than in the papillae of the tongue, where it is known to occur. No data were given to indicate the status of the blood of the patients whose stomachs were examined, and it is not known therefore whether they died in a hematologic relapse or after effective treatment had been given. It is conceivable to us that the gastric mucosa may vary in appearance at different stages of the disease.

Present knowledge concerning the extrinsic factor was summarized by Ungley [2] as follows: Its presence has been confirmed in brewers' yeast, rice polishings, eggs, milk, liver, fraction G of Cohn, liver fractions which are free from protein and polypeptides, and possibly tomatoes. Strauss and Castle postulated (1932) that it might be vitamin B_2,

2. Ungley, C. C.: Some Deficiencies of Nutrition and Their Relation to Disease: II. Nutritional Deficiency in Relation to Anemia, Lancet **1**:875, 925 and 981, 1938.

3. Magnus, H. A., and Ungley, C. C.: The Gastric Lesion in Pernicious Anaemia, Lancet **1**:420, 1938.

but Ungley and James found that this substance was relatively ineffective as a source of the extrinsic factor. It is concluded that vitamin B_6 (the antidermatitic factor in rats) and nicotinic acid are not the extrinsic factor of Castle.

The following data concerning the intrinsic factor of Castle were presented by Ungley. This factor is readily destroyed by heating to 70 or 80 C. for one-half hour; it is not identifiable as hydrochloric acid, pepsin, pepsinogen, rennin or lipase. He considers that his work has disproved Greenspon's theory that the gastric factor potent against pernicious anemia is a hormone effective alone if protected from the action of pepsin. His evidence in this respect was the demonstration that depepsinized gastric juice and pepsin-free extracts of pyloric mucosa have no significant hemopoietic effect unless interaction with a source of the extrinsic factor is allowed. It is his belief that the synthesis of a thermostable product identical with the active principle of liver has not yet been accomplished.

In summarizing the knowledge concerning the active principle of liver he stated that a peptide has been obtained which is twice as potent as the original fraction isolated by Dakin and West. Although kidney is as effective as liver, and brain is about one-third as potent, all attempts to isolate potent fractions from these organs have failed. Ungley considers that the antianemic activity of kidney is not due to the presence of the intrinsic factor, because it is retained after heating to 95 to 100 C. for two hours.

In considering tropical macrocytic anemia, which responds to the administration of autolyzed yeast, Ungley stated that the observations of Wills indicate that this condition is not usually influenced favorably by purified liver extract (anahaemin). He concluded from this that some mechanism other than a deficiency of Castle's intrinsic factor is involved in the production of this syndrome.

According to Wills and Evans,[4] tropical macrocytic anemia resembles pernicious anemia, as the changes in the blood and the alterations in the bone marrow are similar. The cause of tropical anemia is related to that of pernicious anemia, for in the former it at present is regarded as a deficiency state due to the lack of Castle's extrinsic factor, which results in a deficiency in the body of the liver principle that is curative in pernicious anemia. This view is supported by the observation that tropical anemia responds well to treatment with either liver extract or substances such as autolyzed yeast extract which are known to be good sources of the extrinsic factor. Wills and Stewart, in 1935, observed that anemia which was considered to be the animal counter-

4. Wills, L., and Evans, B. D. F.: Tropical Macrocytic Anaemia: Its Relation to Pernicious Anemia, Lancet **2**:416, 1938.

part of tropical anemia could be produced in monkeys by a faulty diet. This anemia responded to autolyzed yeast extract (marmite) by mouth and to liver extracts by oral and parenteral routes. It was found, however, that these animals failed to respond to the more highly purified extracts, even in enormous doses. This led to a study of the action of these refined extracts in tropical anemia in human beings. Clinical trials showed that patients with tropical macrocytic anemia did not respond, as shown by failure of the reticulocytes or red blood cells to increase in number, to the injection of highly purified liver extracts (anahaemin, examen and fractions made from campolon by ammonium sulfate extraction). These preparations are known to be highly potent when given to patients with pernicious anemia. The investigators concluded that this fact further differentiates tropical anemia from pernicious anemia and indicates that there is some new hemopoietic factor present in crude liver preparations and autolyzed yeast products. Judging from their experiments on monkeys, this factor is not vitamin B_1, vitamin B_4, riboflavin or nicotinic acid, but it has not yet been separated from the yeast—fuller's earth filtrate of Edgar and McCrae. It is suggested that the missing factor is some part of the vitamin B complex.

It was stated by Wilkinson, Klein and Ashford [5] that in 1934 Wilkinson and Klein were able to prepare by the action in vitro of certain fractions obtained from hog's stomach on beef, an active protein-free product which resembled the liver principle and was effective when administered parenterally as well as orally. In their recent investigation they have been able to show that stomachs from patients with pernicious anemia, who have or have not received potent antianemic therapy, do not contain an active fraction which they call haemopoietin and which they consider to be identical with the intrinsic factor. This substance was found to be present in normal stomachs when examined under similar conditions. They believe therefore that their observations demonstrate the presence of the antianemic enzyme hemopoietin in the normal stomach and the deficiency of this substance in the stomachs of both treated and untreated patients with pernicious anemia. These observations are in accordance with their theory, already advanced, that the active antianemic principle of liver is elaborated as the result of an interaction between (1) an unknown substance in beef (the extrinsic factor), and (2) the intrinsic factor (hemopoietin). Wilkinson and Klein consider that they have demonstrated the occurrence of this reaction in vitro and also that it takes place in vivo in the normal stomach but not in the stomach of the patient with pernicious anemia.

5. Wilkinson, J. F.; Klein, L., and Ashford, C. A.: The Hematopoietic Activity of the Human Stomach in Pernicious Anemia, Quart. J. Med. **7**:555, 1938.

Morrison [6] reported that patients with pernicious anemia treated with orally administered depepsinized gastric mucosa, prepared by Greenspon's process, showed almost completely negative results. In this observer's opinion the process of depepsinization inactivates the antianemic activity of the gastric mucosa by destroying the intrinsic factor. He concluded further that the role of pepsin in pernicious anemia is not clear and that his investigation has proved only that the process of depepsinization is responsible for the destruction of antianemic activity of the preparations.

As previously stated Klein and Wilkinson,[5] in 1933 and 1934, isolated from hog's stomach concentrated fractions which contained the antianemic factor. Furthermore, when these fractions were incubated with beef, "a relatively thermostable and therapeutically effective concentrate could be made from the products of digestion." Klein and Wilkinson ascribed an enzymic nature to the substance which they call haemopoietin and which they consider to be "identical" with Castle's hypothetic enzyme of gastric juice. They implied that the absence of this substance from the stomach is an important etiologic factor in pernicious anemia. They concluded from their own experiments and those of others that "the site of action of haemopoietin is in the neutral or more alkaline regions of the gastro-intestinal tract rather than in the more acid regions of the stomach."

The experiments of Jones, Grieve and Wilkinson [7] were designed to study further the enzymic properties of fractions of hog's stomach. To accomplish this the interaction of fractions of hog's stomach with myoglobulin from beef and with caseinogen was studied, and the results were compared with those obtained when pepsin was used. The effect of the preparations of hog's stomach was similar to that of pepsin, but there are several interpretations of this observation. Abundant proof exists that hemopoietin and pepsin are not identical, and contamination of the former with the latter must be considered when explaining the similarity of the properties of the two enzymes. A third possibility is that hemopoietin differs from pepsin but has similar properties.

Taylor, Castle, Heinle and Adams [8] have made observations which indicate a similarity between the proteolytic activity of normal human

6. Morrison, S.: A Comparison of Anti-Pernicious Anemia Potency of Depepsinized and Undepepsinized Gastric Mucosa, J. Lab. & Clin. Med. **23**:949, 1938.

7. Jones, T. S. G.; Grieve, W. S. M., and Wilkinson, J. F.: Investigations on the Nature of Haemopoietin, the Anti-Anaemic Principle in Hog's Stomach: The Interaction of Haemopoietin and Pepsin with Myoglobulin and Caseinogen, Biochem. J. **32**:665, 1938.

8. Taylor, F. H. L.; Castle, W. B.; Heinle, R. W., and Adams, M. A.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: Resemblances Between Proteolytic Activity of Normal Human Gastric Juice on Casein in Neutral Solution and Activity of Intrinsic Factor, J. Clin. Investigation **17**:335, 1938.

gastric juice on casein in neutral solution and the activity of the intrinsic factor. They have observed that incubation of gastric juice and a casein solution at 37.5 C. and a p_H of 7.4 results in a progressive increase in the nitrogenous substances in the trichloroacetic filtrates of these digests. Furthermore, the activity of both the gastric secretions and the intrinsic factor is not dependent on the presence of saliva or regurgitated duodenal contents; both types of activity are absent or greatly diminished in the gastric secretion of patients with addisonian pernicious anemia; they are not destroyed by Berkefeld filtration or exposure to alkali; they are both destroyed by exposure to 40 C. for seventy-two hours and to 70 to 80 C. for thirty minutes or by baking for five minutes and are inhibited by an acidity greater than p_H 3.5. The in vitro activity of normal human gastric juice is entirely eliminated by contact with Lloyd's reagent (specially prepared siliceous earth), whereas others have stated that this substance removes only a portion of the intrinsic factor. This study indicates, as one might anticipate, that the proteolytic activity of gastric juice and the activity of the intrinsic factor are influenced by similar alterations in their environment. As they are both produced by the stomach, it seems logical to assume, in our opinion, that they would be susceptible to the same physical and chemical influences.

Bachrach and Fogelson,[9] after a careful review of the literature, came to the conclusion, with which we are in accord, that no normal laboratory animal has yet been found which exhibits a sufficiently uniform or characteristic reaction to antianemic substances to permit its use for assay purposes. For a period of two years they observed 7 dogs from which 30 cm. of jejunum, the duodenum and the distal seven-eighths of the stomach had been removed. The experimental animals recovered rapidly from the operation and within a few months were indistinguishable from normal animals. At no time did any of the 7 animals show a blood picture even suggestive of pernicious anemia, although they all had transient "secondary anemia," from which all but 1 recovered. Although these investigators failed to accomplish their purpose, nevertheless their results are of great theoretic importance. As they pointed out, the changes in the blood should have succeeded if Meulengracht's hypothesis had been applicable to the dog. Their results show clearly that it is not, for he submitted evidence which indicated that the intrinsic factor of Castle has its source chiefly in the pyloric glands of the stomach and the glands of Brunner in the small intestine. The observations of Fogelson and Bachrach indicated that if the source of the intrinsic factor in the dog is the "pyloric gland organ," other parts of the body must participate in this function.

9. Bachrach, W. H., and Fogelson, S. J.: The Role of the Upper Gastrointestinal Tract in the Etiology of Pernicious Anemia, J. Lab. & Clin. Med. **24**:249, 1938.

Potent liver extract was examined by Jacobs [10] for the presence of choline, because he had previously reported that a reticulocyte response had been observed following the oral administration of potato juice and tyrosine. For this reason he thought it justifiable to examine liver extract to determine whether or not some of the simpler nitrogenous bases, such as choline, were present, as they are known to occur in potatoes and other plants. It was determined that at least 1 per cent of choline was present in one preparation of liver extract for oral administration,[11] and studies are contemplated to investigate the rather remote possibility of its effect on pernicious anemia.

Jequier and Apsey [12] consider that there was evidence which suggested that as the antianemic principle was widely diffused throughout the body and in the kidney, it should be eliminated in the urine, like so many hormones. If this could be established, it would be of interest, first, in indicating that the metabolism of the principle is not confined to the alimentary tract and liver, and, second, it would be of possible diagnostic importance, for the principle might be absent from the urine of patients with pernicious anemia. It was determined that the urine of untreated patients with pernicious anemia, as well as normal urine, contained a substance which when injected subcutaneously provoked a reticulocyte response in the white rat. In our opinion, however, the accuracy of this conclusion may be challenged, as the reticulocyte counts were recorded for only three to five days after the injection, and the maximum increase shown was 4.0 per cent. One patient with pernicious anemia, whose red blood cell count was 1,820,000 per cubic millimeter, was given a drop by drop rectal infusion of 300 to 500 cc. of normal urine, which was repeated twice. This was not followed by an increase in the reticulocyte count or evidence of subjective improvement. The patient subsequently responded satisfactorily to the injection of potent liver extract. They concluded that human urine contains a substance capable of producing a reticulocyte response in the white rat. Normal urine, however, showed no therapeutic activity in 1 case of pernicious anemia.

Schiff, Rich and Simon [13] studied the hemopoietic effect of injections of extracts prepared from the livers of 3 patients with cirrhosis of the liver who had macrocytic anemia. Two of them had hepatic cirrhosis,

10. Jacobs, H. R.: On the Nature of the Antipernicious Anemia Principle: Search for Nitrogenous Bases Isolation of Choline, J. Lab. & Clin. Med. **24**: 128, 1938.

11. The liver extract used was that prepared by Eli Lilly & Co.

12. Jequier, E., and Apsey, G. R. M.: Anti-Pernicious Anemia Principle: Some Experiments with Urine, Brit. M. J. **2**:934, 1938.

13. Schiff, L.; Rich, M. L., and Simon, S. D.: The "Hematopoietic Principle" in the Diseased Human Liver, Am. J. M. Sc. **196**:313, 1938.

and the third had carcinoma of the hepatic duct with cirrhosis and hepatic metastases. Each patient had definite macrocytic anemia; 1 had received treatment with a commercial liver extract preparation a month before death, without effect; the second patient "had at no time during his illness received antianemic therapy other than iron;" no statement was made about antianemic therapy in the third case. When liver extract was made from the diseased livers of these 3 patients and given intramuscularly to untreated patients with pernicious anemia, characteristic reticulocytosis and an increase in the hemoglobin value and red blood cell count resulted. It was concluded from these experiments that human liver may contain the specific hemopoietic principle even when extensively diseased and that this statement holds true even when a patient with diseased liver has associated macrocytic anemia. Naturally, these experiments suggested that the macrocytic anemia associated with hepatic disease is not caused by failure of the liver to store the specific antianemic substance. Their results are at variance with those reported by Goldhamer, Isaacs and Sturgis in 1934, who observed that an extract prepared post mortem from the liver of a patient with cirrhosis and macrocytic anemia was ineffective in eliciting a hemopoietic response when administered parenterally to a patient with pernicious anemia in relapse. The studies by Schiff and his collaborators suggested strongly that macrocytic anemia in a patient with cirrhosis of the liver must, in some instances, be due to causes other than an inability of the liver to store the hemopoietic principle, but they did not offer an explanation of this. The fact that an extensively diseased liver which contains the active principle may be present in a patient with macrocytic anemia was noted by Goldhamer and his associates in their original publication.

Pernicious anemia is now believed to be caused by simple deficiency of a substance which is required specifically for the maturation of erythropoietic cells, but previously it was commonly supposed to be a hemolytic anemia. In order to clarify the nature of the mechanism of this anemia, the rate of excretion of coproporphyrin I as an index of the activity of the bone marrow and, concurrently, the quantitative measurements of urobilin excretion have been made by Dobriner and Rhoads[14] to estimate the rate of blood destruction. By studying the coproporphyrin I and urobilin excretion of patients with pernicious anemia in relapse and during therapeutically induced remissions, they reached the following conclusions: 1. During relapse, erythrocytes are being formed and also destroyed more rapidly. 2. During a remission the rate of destruction returns quickly to normal, and at the same time the rate of formation becomes less. These observations are interpreted

14. Dobriner, K., and Rhoads, C. P.: Metabolism of Blood Pigments in Pernicious Anemia, J. Clin. Investigation **17**:95, 1938.

to indicate that hemolysis is a factor in pernicious anemia. The authors do not regard this concept as incompatible with the etiologic mechanism described by Castle, as they stated that "it suggests only that the Castle mechanism should include hemolysis operative only in the presence of a deficiency."

Rhoads and Miller [15] observed that the combination of aminopyrine and a diet producing black tongue caused anemia in dogs. This suggested that indole, as a representative of the aromatic compounds, produced by endogenous metabolism, might have a similar action on the blood. It is believed that indole is converted into indican by the liver and excreted by the kidneys, as indicated by its presence in the urine and its accumulation in the blood after the removal of both kidneys. Anemia in mice has been observed after the injection of indole. Also, indicanuria and anemia which is amenable to liver extract therapy have been produced in dogs which have had surgically formed, inactive, open jejunal segments. Rhoads and Miller observed that the feeding of indole to dogs ingesting a normal diet results occasionally in mild anemia. The combination of indole and a diet producing black tongue causes an anemia which can be cured by adding liver extract orally or by substituting a normal intake of food for the deficient one. Neither indole alone nor an abnormal diet produces marked anemia in experimental animals.

Additional studies were made by these authors [16] to determine the mechanism of production of anemia caused by the effect of indole and a deficient diet. They concluded that the hemolysis caused by indole is enhanced by a deficient diet; that the hemolytic effect can be abolished by supplementing the deficient diet with potent antianemic liver extract; that hemolysis affects all the types of red blood cells, including reticulocytes, and that recovery from the anemia is associated with cessation of the hemolytic process. Although the hemolytic process is an active one in the causation of the anemia, the authors also stated that "an abnormally low rate of production of erythrocytes may well be a factor in the production of the anemia."

Ponder and Rhoads [17] found that with saponin, sodium taurocholate at a p_H of 7.0, or sodium glycocholate at a p_H of 6.0, the red blood cells from a patient with pernicious anemia were more vulnerable in vitro than normal cells. During the development of a remission the resistance of the cells returned slowly to normal.

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15. Rhoads, C. P., and Miller, D. K.: Induced Susceptibility of Blood to Indol, J. Exper. Med. **67**:273, 1938.

16. Rhoads, C. P.; Barker, W. H., and Miller, D. K.: Increased Susceptibility to Hemolysis by Indol in Dogs Fed Deficient Diets, J. Exper. Med. **67**:299, 1938.

17. Ponder, E., and Rhoads, C. P.: Red Cell Resistance to Lysins in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **38**:540, 1938.

Kirk [18] noted abnormally low total phosphatide values in the plasma of patients with pernicious anemia in relapse. After liver therapy for two to four weeks, this value increased, as well as the concentration of ether-insoluble phosphatide of the plasma, and the cerebrosides of the corpuscles. No characteristic differences marked the patients with involvement of the spinal cord.

De Lucia and Russo [19] observed a diminution in the total acid-soluble and lipoid phosphorus in all forms of anemia. The inorganic phosphorus was the most variable of the group. In cases of pernicious anemia in which liver preparations were given, there was a definite increase in the total and acid-soluble phosphorus, while the lipoid fraction increased slowly.

Mansfeld and Sos [20] found that liver extract would cause regeneration of the blood in rabbits made anemic by repeated injections of small amounts of saponin, only if the thyroid gland was present. After thyroidectomy the response could not be obtained unless a protein-free extract of hydrolyzed thyroid gland was injected. This substance, independent of thyroxin, was designated as the myelotropic hormone of the thyroid. Thyroidectomy did not interfere with the activity of stomach extract.

Groen [21] found diminished absorption of dextrose in 3 patients with pernicious anemia during relapse. The absorption returned to normal after treatment.

Schneiderbauer [22] described 3 cases of chronic deforming polyarthritis in which pernicious anemia developed. The author attributed the pernicious anemia to infectious chronic gastritis, which was considered to be an extension or a part of the infectious process involving the joints.

From observations on 38 patients with pernicious anemia, van der Scheer and Koek [23] concluded that polyneuritis, with corresponding symptoms, was present in some cases. Histologic studies confirmed the view that in pernicious anemia lesions of the peripheral nerves may occur, as well as those of the central nervous system.

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18. Kirk, E.: The Concentration of the Individual Phosphatides (Ether-Insoluble Phosphatide, Lecithin and Kephalin) and of Cerebrosides in Plasma and Red Blood Cells in Normal Individuals, and in Pernicious Anemia, Acta med. Scandinav., 1938, supp, 89, p. 198.

19. de Lucia, P., and Russo, P.: Il quadro del fosforo ematico nell'anemia, Boll. Soc. ital. di biol. sper. **13**:701, 1938.

20. Mansfeld, G., and Sos, J.: Ueber die Beziehungen der Schilddrüse zur perniziösen Anämie, Klin. Wchnschr. **17**:386, 1938.

21. Groen, J.: Absorption of Glucose from the Small Intestine in Deficiency Disease, New England, J. Med. **218**:247, 1938.

22. Schneiderbauer, A.: Perniziöse Anämie in Verlaufe von chronischer Polyarthritis, Ztschr. f. klin. Med. **134**:113, 1938.

23. van der Scheer, W. M., and Koek, H. C.: Peripheral Nerve Lesions in Cases of Pernicious Anemia, Acta psychiat. et neurol. **13**:61, 1938.

Haring [24] studied polyps of the gastric mucosa in pernicious anemia. Histologically they resemble adenomas of the thyroid gland which occur in cases of exophthalmic goiter or myxedema, and the author suggested that they may be related to incretory activity. A relation between gastric polyposis and pernicious anemia was postulated, and the presence of gastric polyps should lead to study of the patient for possible hyperchromic anemia.

Luhr and Gulzow [25] made gastroscopic studies of patients with pernicious anemia and noted atrophic processes and acute and chronic gastritic lesions. The authors believe that gastritis plays an important part in the pathogenesis of pernicious anemia and that this accounts for the increased protein content of the gastric juice of these patients.

Wintrobe [26] and his collaborators observed young pigs which were fed a diet which was adequate in all respects. As the animals developed, the amount of yeast which was fed was gradually reduced, and thiamin (vitamin B_1) and riboflavin were substituted for it. Ataxia and loss of reflexes resulted but the motor power of the muscles remained intact. These changes suggested the presence of a sensory defect, which was substantiated at necropsy. There was selective degeneration of the peripheral sensory neuron, involving its cell body in the posterior root ganglion and the peripheral axon. The central axon which was included in the posterior roots and in the posterior columns was likewise affected. There were no clearcut abnormalities in the anterior roots or anterior horn cells. It was thought that these changes were due to a deficiency of one or more components of the vitamin B complex. In further experiments, which are now in progress, the significance of riboflavin, nicotinic acid, vitamin B_6 and other components of the vitamin B_2 complex is being studied. The relation of the neurologic changes observed to those occurring in pernicious anemia and pellagra is a matter only for speculation. The peripheral neuritis and changes in the posterior columns without glial reaction were similar to those seen in subacute combined degeneration of the cord, but in no instance were any changes observed in the lateral columns. The authors properly emphasized, however, that in human beings nutritional deficiencies are usually multiple in character and are therefore not entirely comparable to the experimental dietary defects to which the experimental animals were subjected.

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24. Haring, W.: Gutartige Magengeschwülste bei perniziöser Anämie, München. med. Wchnschr. **85**:1544, 1938.

25. Luhr, K., and Gulzow, M.: Gastritisbefunde bei der Achylia perniciösa: Gastroskopische Untersuchungen, Deutsches Arch. f. klin. Med. **182**:327, 1938.

26. Wintrobe, M. M.; Mitchell, D. M., and Kolb, L. C.: Sensory Neuron Degeneration in Vitamin Deficiency: Degeneration of Posterior Columns of Spinal Cord, Peripheral Nerves, and Dorsal Root Ganglion Cells in Young Pigs Fed Diet Containing Thiamin (B_1) and Riboflavin But Otherwise Deficient in Vitamin B Complex, J. Exper. Med. **68**:207, 1938.

Suh and Merritt [27] stated that the classic triad of pernicious anemia is hyperchromic anemia, degenerative changes in the spinal cord and defective gastric secretion. They suggested that the changes in the spinal cord may be related to some unknown factor which is independent of the changes in the blood and the achylia gastrica. This may be a defect in absorption of vitamin B, as "suggested by the fact that most of the reported cases have been associated with the conditions which might be accompanied by such a defect." Eight cases of subacute combined degeneration of the spinal cord without macrocytic anemia are reported. The common causes of changes in the posterior and lateral tracts of the spinal cord which produce changes closely resembling those of subacute combined degeneration of the cord, as seen in pernicious anemia, are multiple sclerosis, syphilitic meningomyelitis, syringomyelia and tumors of the spinal cord. These conditions, as well as pernicious anemia, were excluded as far as possible in their reported cases. Three of their patients presented the typical neurologic syndrome associated with pernicious anemia, but there was no significant disturbance of the blood or achylia gastrica. In 1 patient there was outstanding evidence of involvement of both posterior and lateral tracts of the spinal cord. In 3 additional patients there was conclusive evidence of subacute combined degeneration, but in each case there was normal gastric acidity and the anemia was hypochromic in type. In 1 patient there were mild hypochromic anemia, achylia gastrica and evidence of endocrine dysfunction (the syndrome of adiposa dolorosa). The complicating factors were: arteriosclerosis in 3 cases, Hodgkin's disease in 1, ulcerative colitis in 1 and glandular dysfunction (adiposa dolorosa) in 1. These observers postulated that an impaired utilization of vitamin B is the most plausible explanation of the symptoms referable to the spinal cord in cases of pernicious anemia. The same factor is the most probable cause of the symptoms and signs of the 8 patients who were observed. It is suggested that this type of disease of the spinal cord is only symptomatic of various disease conditions.

Therapy.—Von Bonsdorff [28] found that powdered Bothriocephalus latus inactivated liver extract, and a similar action in the gastrointestinal tract was postulated. Tötterman [29] found that on feeding the powder to

27. Suh, T., and Merritt, H. H.: Combined System Disease Without Obvious Evidence of Pernicious (Macrocytic) Anemia: Report of Eight Cases; One Autopsy, Am. J. M. Sc. **196**:57, 1938.

28. von Bonsdorff, B.: Wird der antianämische Faktor in Leberpräparaten vom Bothriocephalus latus zerstört? Acta med. Scandinav. **89**:153, 1938.

29. Tötterman, G.: Experimental Researches upon the Role of Bothriocephalus Latus in the Pathogenesis of Pernicious Anemia, Acta med. Scandinav., 1938, supp. 89, p. 150; Ueber die Pathogenese der Wurmanämie, ibid. **96**:268, 1938.

patients with anemia due to Bothriocephalus a more severe anemia, with a high color index, developed in 5 of 8 patients. On discontinuance of the use of the powder, the patients recovered. This anemia was not produced in normal persons or in patients with pernicious anemia who were receiving liver or stomach treatment.

Emile Weil [30] has formulated what he characterizes as *le terrain morbide* in pernicious anemia and in aplastic states of the marrow. These include certain hereditary and familial characteristics; gastrointestinal abnormalities, with achlorhydria and achylia, and a certain susceptibility on the part of the bone marrow. In the presence of the proper "soil," certain external factors influence the development of the anemia.

Hanssen [31] commented on the fact that pernicious anemia is not frequent in Norway. It is rare in the three northern counties. In the north and west the rate is 2 per hundred thousand population, while in the east and south it is 4 to 6 per hundred thousand. The death rate for all ages has fallen since 1927, except for patients over 70 years of age, who have shown an increase in rate.

Standards for increases in the red blood cell count after intramuscular liver therapy and after stomach therapy in pernicious anemia were calculated by Isaacs, Bethell, Riddle and Friedman.[32] From the graphs it is possible to determine a standard response expected at weekly intervals. Under ideal conditions a normal red blood cell count is reached in eight weeks with intramuscular therapy.

Standards for the maximum reticulocyte percentage after liver therapy intramuscularly in cases of pernicious anemia were published by Isaacs and Friedman.[33] It was found that the maximum reticulocyte percentage could be expressed by the formula $\frac{82 - 22\ Eo.}{1 + 0.5\ Eo.}$ (*Eo.* equaling the initial red blood cell count in millions per cubic millimeter).

Mills and Mawson [34] noted that the blood content of bilirubin (van den Bergh reaction) was increased in pernicious anemia during relapse but was lowered after therapy. The average concentration in 85 cases was 0.98 ± 0.06 mg. per hundred cubic centimeters. Ninety-three per

30. Weil, P. E.: Le terrain morbide dans le biermer et les états d'aplasie médullaire, in Comptes rendus de la troisième Conférence internationale de pathologie géographique, Helsingfors, Mercators Tryckeri, 1937, p. 193.

31. Hanssen, O.: The Decrease in Mortality from Pernicious Anaemia in Norway, Acta med. Scandinav., 1938, supp. 90, p. 436.

32. Isaacs, R.; Bethell, F. H.; Riddle, M. C., and Friedman, A.: Standards for Red Blood Cell Increase After Liver and Stomach Therapy in Pernicious Anemia, J. A. M. A. **111**:2291 (Dec. 17) 1938

33. Isaacs, R., and Friedman, A.: Standards for Maximum Reticulocyte Percentage After Intramuscular Liver Therapy in Pernicious Anemia, Am. J. M. Sc. **196**:718, 1938.

34. Mills, J., and Mawson, C. A.: Significance of the van den Bergh Reaction in the Diagnosis of Pernicious Anemia, Lancet **2**:1455, 1938.

cent of the values were greater than 0.4 mg., whereas 91 per cent of a normal control group had values less than 0.4 mg. (average of 0.1 ± 0.02 mg.).

Fouts and Helmer [35] found a marked increase in the urea clearance of patients with pernicious anemia after a remission induced with liver extract. Patients with complications accompanied by a low value for urea clearance required a larger dose of liver extract to maintain a normal red blood cell count.

Castellani [36] compared the symptoms of sprue and pernicious anemia. The rhamnose test gave a negative reaction in the former and a positive reaction in the latter.

From a study of forty-five specimens of bone marrow taken from patients with various stages of pernicious anemia, Jones [37] concluded that the megaloblast series of cells form a separate group and die off during liver therapy, being replaced by cells of the normoblast series.

Vesa [38] studied the heart in pernicious anemia. Numerous circulatory disturbances were noted, but only slight changes were apparent in the electrocardiogram. The heart was often enlarged but without a mitral configuration. A murmur was common. Because of the advanced ages of some of the patients, the etiologic relation of the changes was uncertain. After exertion the electrocardiogram showed some changes suggestive of coronary insufficiency, but they were less marked than in coronary stenosis.

Kampmeier and Jones [39] noted that visual symptoms due to atrophy of the optic nerve may be the presenting symptom or an important symptom in pernicious anemia. The symptoms in 3 cases demonstrated the necessity of ruling out the possibility of tabes dorsalis.

Goldstein [40] has summarized the history of the developments of liver therapy in pernicious anemia, tracing it back to 1552.

Okada, Shamoto and Yamase [41] found a substance in spinach which exerted a limited hemopoietic action in a patient with pernicious anemia. They suggested spinach therapy as an adjuvant to liver or stomach treatment.

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35. Fouts, P. J., and Helmer, O. M.: Urea Clearance in Pernicious Anemia, Arch. Int. Med. **61**:87 (Jan.) 1938.

36. Castellani, A.: Sprue and Pernicious Anemia, Rev. Gastroenterol. **5**: 226, 1938.

37. Jones, O. P.: Nature of the Reticulocytosis in Pernicious Anemia Following Liver Therapy, Proc. Soc. Exper. Biol. & Med. **38**:222, 1938.

38. Vesa, A.: Herzsymptome bei Anämien, Acta med. Scandinav., 1938, supp. 89, p. 182.

39. Kampmeier, R. H., and Jones, E.: Optic Atrophy in Pernicious Anemia, Am. J. M. Sc. **195**:633, 1938.

40. Goldstein, H. I.: Liver Therapy in Anemia, M. World **56**:244, 1938.

41. Okada, S.; Shamoto, M., and Yamase, F.: New Therapy in Pernicious Anemia, Nagoya J. M. Sc. **11**:147, 1937.

Krantz [42] noted the development of marked allergic phenomena in a patient with pernicious anemia who was treated with liver extract intramuscularly. The patient originally had not shown the expected hemopoietic response when treated orally. Small but increasing amounts of liver extract given intramuscularly eliminated the reactions. Gardner [43] described a similar condition in which the patient was sensitive to liver products taken orally. In Criep's [44] case the patient acquired sensitivity to liver extract but later was able to tolerate it. Positive cutaneous reactions and reagins were present for at least three months after the initial reaction.

Massobrio and Maranzana [45] made additional studies on the eosinophilia developing in normal persons and in patients with pernicious anemia after liver therapy. It appeared when the liver was raw or almost raw but not when it was thoroughly cooked or when an extract was injected. Schemm [46] has outlined the practical details in the management of pernicious anemia. The average cost of medication is about $10 per year. The total cost to the patient varies from $110 to $170 per year when the intramuscular method of treatment is employed. Case histories of 4 brothers with pernicious anemia were cited. Sturgis,[47] from observations on 1,000 patients with pernicious anemia, outlined seven points in the diagnosis of the disease: (*a*) achlorhydria, (*b*) macrocytosis, (*c*) a high color index, (*d*) the response to therapy, (*e*) paresthesia, (*f*) glossitis and (*g*) leukopenia or the absence of leukocytosis. The most satisfactory method of treatment is by the intramuscular administration of liver extract. Hansen-Prüss [48] was unable to produce a remission in pernicious anemia, hypochromic anemia, myeloid anemia, idiopathic hypochromic anemia or hypochromic anemia in hepatic disease with the intramuscular or intravenous injection of nicotinic acid in doses of 60 mg. per day. After treatment a fall in the white blood cell count of the marrow was noted.

The hemopoietic principle of liver extract is not precipitated by calcium carbonate ($CaCl_2 + Na_2CO_3$) but is absorbed by norite char-

42. Krantz, C. I.: Anaphylactic Reactions Following Medication with Parenteral Liver Extract, J. A. M. A. **110**:802 (March 12) 1938.

43. Gardner, J. W.: Allergy to Oral Administration of Liver Concentrate, J. A. M. A. **110**:2003 (June 11) 1938.

44. Criep, L. H.: Allergy to Liver Extract, J. A. M. A. **110**:507 (Feb. 12) 1938.

45. Massobrio, E., and Maranzana, P.: L'eosinofilia da ingestione di fegato; Ricerche cliniche e sperimentali, Arch. per le sc. med. **65**:201, 1938.

46. Schemm, F. R.: The Management of Pernicious Anemia in Private Practice, Journal-Lancet **58**:63, 1938.

47. Sturgis, C. C.: Remarks on the Differential Diagnosis and Treatment of Pernicious Anemia, Bull. New York Acad. Med. **14**:715, 1938.

48. Hansen-Prüss, O. C.: Failure of Nicotinic Acid in the Treatment of Anemia, New England J. Med. **218**:1050, 1938.

coal. Sladek and Kyer [49] found that this extract contains tyrosine. There was 0.41 to 0.91 per cent nitrogen. Jacobs [10] found that liver extract contains 1 per cent choline.

Karrer, Frei and Ringier [50] found that extraction of phosphorus, pentose and most of the purine content did not reduce the hemopoietic activity of liver extract. The active material did not contain flavin, pterine, reducing carbohydrate, polypeptides, aminoacetic acid, phenylalanine, tyrosine, histidine or oxyprolin. Analysis of an active fraction showed carbon, 45.68 per cent; hydrogen, 6.75 per cent; nitrogen, 14.5 per cent, and some sulfur. Mazza and Penati [51] found that neither nucleic acid nor xanthopterin was therapeutically effective in 3 cases of pernicious anemia. The urine contained a normal amount of pterine.

Neurologic and Cerebral Manifestations in Pernicious Anemia.—The frequent occurrence of manifestations in the central nervous system in pernicious anemia has led to the acceptance of the axiom that if neurologic complications are absent in a case of macrocytic anemia, although pernicious anemia is a possibility, other causes should be immediately investigated. In the series of 69 patients reported on by Kampmeier and Jones,[39] 75 per cent showed involvement of the central nervous system. These figures were well within the range that had been reported previously. The cause of the changes in the nervous system remains in the realm of theory. Robinson [52] considers that pernicious anemia is a third psychogenic disease and has suggested that it is due to a degenerative lesion of the brain. The neurologic manifestations are considered by Suh and Merritt [27] to be the result of vitamin B deficiency. Drake [53] carefully studied a patient with pernicious anemia who showed subacute combined degeneration of the spinal cord and concluded from his results that this complication is directly related to the anemia. This observation is directly opposed to the findings of Suh and Merritt, who reported a series of cases of combined system disease without obvious evidence of pernicious (macrocytic) anemia. That the blood supply (anemia) may have some influence on the function of the central nervous system gains support from the experiments of Bar-

49. Sladek, J., and Kyer, J.: Preparation and Properties of the Charcoal Adsorbate of Liver Extract, Proc. Soc. Exper. Biol. & Med. **39**:227, 1938.

50. Karrer, P.; Frei, P., and Ringier, B. H.: Bestandteile von gegen perniziöse Anämie hoch aktiven Leberpräparaten: II., Helvet. chim. acta **21**:314, 1938.

51. Mazza, F. P., and Penati, F.: Sulla natura chimica del principio antipernicioso del fegato, Arch. di sc. biol. **24**:83, 1938.

52. Robinson, S. C.: Exophthalmic Goitre and Gastroduodenal Ulcer—Two Constitutionally Different Diseases, with a Note on Pernicious Anemia, Illinois M. J. **73**:210, 1938.

53. Drake, E. H.: Pernicious Anemia with Subacute Combined Lateral Sclerosis, Maine M. J. **29**:110, 1938.

geton.[54] This investigator demonstrated that the transmission of impulses through a sympathetic ganglion could be influenced by varying the blood supply. A specific neurotoxin due to a disturbance in lipid metabolism has also been considered the causative factor of the pathologic changes in the cord.

The most common neurologic symptoms are numbness and tingling of the extremities, coldness, burning, ataxia, loss of finer coordination of the fingers and disturbances of the bowel and bladder. Careful studies of the function of the bladder and the need of treatment for this complication have been emphasized by Kickham and Moloney.[55] These authors stated that the course may be accurately ascertained by cystometric observations. Van der Scheer and Koek [23] have observed 38 patients with pernicious anemia, and it is their opinion that the symptoms frequently noted are due to changes in the peripheral nerves rather than to alterations in the cord. In biopsy and autopsy specimens they have demonstrated myelin degeneration, which occurs usually at the periphery and tends to diminish in severity proximally. Yang and Chang,[56] who reported the occurrence of pernicious anemia in a Chinese, also concluded from their work that the neurologic manifestations may be due to pathologic changes in the peripheral nerves.

The signs are dependent on the site of the lesion (peripheral or central) and the extent of the pathologic involvement. The degeneration in the spinal cord may be in the anterior, lateral or posterior columns. These tracts may be involved alone or simultaneously. As a result, the reflexes may be intensified, decreased or absent. No specific mental picture has been observed in pernicious anemia, although cerebral involvement is common. Many investigators are of the opinion that the mental manifestations are independent of the disease process of pernicious anemia. Romano and Evans [57] cited a case of secondary anemia associated with a psychosis. The mental symptoms improved with the elimination of the anemia. These authors believe that this same process occurs in pernicious anemia. Rotter and Peña Chavarría [58] have studied the influence of tropical anemias on the physiopathologic state of the brain. It is their opinion that the anemia, nutritional dis-

54. Bargeton, D.: Some Effects of Acute Anemia on the Transmission of Impulses Through a Sympathetic Ganglion, Am. J. Physiol. **121**:261, 1938.

55. Kickham, C. J. E., and Moloney, W. C.: Disturbances of Bladder Function in Pernicious Anemia, New England J. Med. **218**:880, 1938.

56. Yang, C. S., and Chang, S. L.: The Treatment of Neurological Manifestations of Pernicious Anemia: Report of a Case, Chinese M. J. **53**:469, 1938.

57. Romano, J., and Evans, J. W.: Symptomatic Psychosis in a Case of Secondary Anemia, Arch. Neurol. & Psychiat. **39**:1294 (June) 1938.

58. Rotter, W., and Peña Chavarría, A.: The Influence of the Tropical Anemias on the Physiopathology of the Brain, Puerto Rico J. Pub. Health & Trop. Med. **13**:359, 1938.

orders and etiologic factors (malaria and ankylostoma) must all be considered as causes of the mental disturbances.

Ungley [59] has recently published a comprehensive review on the prevention and treatment of the neurologic manifestations. He has emphasized that an early and accurate diagnosis should be made; excess antianemic treatment, with the blood picture as an index, should be given; beneficial changes, if they occur, will be observed before one year, and the prognosis depends more on the duration of the illness and less on the severity of the disease and the age of the patient. He concluded that cure is a rarity and is not to be expected.

Gastric Juice.—Although it has been adequately demonstrated that the gastric juice is an important factor in hemopoiesis, there still exist several problems related to this subject which have been unanswered. What is the intrinsic factor? Where is its source? What is its modus operandi? Morrison [60] has summarized the various hypothetic suggestions related to these questions but has added that further investigations are needed to evaluate the theories.

Final proof of the role of the stomach in hemopoiesis has been demonstrated by Wilkinson and his co-workers.[5] These investigators incubated with beef steak stomachs of patients with a normal blood picture and of patients with pernicious anemia and noted that in the former cases this was effective but not in the latter. They concluded that the "enzyme" is absent from the stomach in pernicious anemia or present in too small amounts to be detected by this method.

In regard to the source of the intrinsic factor, Magnus and Ungley [3] pointed out that the pathologic changes in the stomachs of patients who die of pernicious anemia are limited to the fundus. This fact is somewhat disconcerting, since it had been previously demonstrated from a histologic and a physiologic point of view that the pylorus, cardia and duodenum were the important sites of formation. It is the opinion of Uotila [61] that the small intestine has more antianemic principle than the stomach and that it plays an important part in the preparation of the antianemic substance. This author fed to different patients a powdered preparation made from various parts of the small intestine. He concluded that the antianemic substance was present throughout the small intestine and that its strength of activity varied in the ileum, duodenum and jejunum in decreasing order. Goodfriend, Chain and

59. Ungley, C. C.: The Prevention and Treatment of the Neurological Manifestations of Pernicious Anemia, Clin. J. **67**:5, 1938.

60. Morrison, S.: Newer Interpretations and Conceptions of Gastric Mucosal Functions: Further Advances in Study of Gastric Achylia; Evidence Suggesting Role for Oxyntic Cell in Pernicious Anemia, Internat. Clin. **1**:119, 1938.

61. Uotila, U.: On the Antianemic Function of the Small Intestine, Acta med. Scandinav. **95**:415, 1938.

Florey [62] attempted to evaluate the antianemic potency of various gastrointestinal secretions according to the method of Jacobson. They found an effective reticulocytogenic agent for guinea pigs in the pyloric, duodenal and ileal secretions of the pig and in the pyloric and duodenal contents of the rabbit and goat; this factor was absent from the fundus of the pig and cat. They are of the opinion that these findings substantiate those of Meulengracht as to the source and distribution of the intrinsic factor.

Goldhamer and Kyer [63] were able to salt out the intrinsic factor from hog stomach and gastric juice with ammonium sulfate. It was further observed by these authors that this substance was nondialyzable. Depepsinized gastric mucosa was found by Morrison [6] to be ineffective, but whole stomach mucosa contained an active erythropoietic substance. From the results obtained, this author concluded that pepsin per se is not the inactivating material, but, rather, the process of eliminating the pepsin also inactivates the mucosa. Jones and Wilkinson [64] attempted to determine the quantity of intrinsic factor in gastric juice by the Lasch method. They concluded that the method was unreliable and that all gastric juices showed similar activity curves as regards the p_H.

Taylor and his co-workers [8] studied the resemblance between the proteolytic activity of normal human gastric juice on casein in neutral solution and the activity of the intrinsic factor. When equal parts of gastric juice and a 1 per cent solution of casein was incubated at 37.5 C. and at p_H 7.4, there was a progressive increase in the nitrogenous substances in trichloroacetic filtrates of the digests. This activity was found to be independent of saliva or duodenal contents; it was absent or diminished in patients with pernicious anemia; the activity was not altered by Berkefeld filtration or exposure to alkali but was destroyed by heating at 40 C. for seventy-two hours or at 70 to 80 C. for thirty minutes or by boiling for five minutes. The activity was somewhat inhibited by p_H less than 3.5. The in vitro activity of the mixture was removed by exposure to Lloyd's reagent (specially prepared siliceous earth). The hydrolysis of casein under the conditions described progresses within twenty-four hours to proteoses and peptones, with the production of very little amino nitrogen. The authors concluded that

62. Goodfriend, J.; Chain, E., and Florey, H. W.: A Reticulocytogenic Agent for Guinea Pigs Present in Certain Gastro-Intestinal Secretions, Quart. J. Exper. Physiol. **28**:115, 1938.

63. Goldhamer, S. M., and Kyer, J.: Chemical Studies of the Intrinsic Factor in Desiccated Stomach and Normal Human Gastric Juice: I. Separation of the Intrinsic Factor, Proc. Soc. Exper. Biol. & Med. **37**:659, 1938.

64. Jones, T. S. G., and Wilkinson, J. F.: Investigations on the Nature of Haemopoietin, the Anti-Anaemic Principle in Hog's Stomach: IV. On the Biochemical Method of Lasch for the Quantitative Determination of the "Intrinsic Factor" in Gastric Juice, Biochem. J. **32**:1352, 1938.

the activity described is not due to pepsin, trypsin or erepsin and that the results indicate the activity of a proteolytic enzyme.

Further evidence that achlorhydria is a constant feature of pernicious anemia was demonstrated by Rozendaal and Washburn.[65] They observed 906 patients with pernicious anemia, and all had achlorhydria, in both relapse and remission. In 34 instances the absence of "free" acid was observed two to twenty-one years before anemia was present; in 2 other cases, hydrochloric acid was noted seventeen to nineteen years before the anemia was observed.

An excellent summary of the role of the various parts of the gastrointestinal tract in the formation of red blood cells and in the prevention of anemia has been published by Kugelmass.[66]

MACROCYTIC ANEMIAS OTHER THAN PERNICIOUS ANEMIA

The relation of the gastrointestinal tract to the physiology of erythropoiesis has received considerabe emphasis in the past decade. The various factors which may produce macrocytic anemia have been discussed in the excellent reviews by Vaughan,[67] Ungley [2] and Davidson.[68] It is generally accepted that the substance necessary for maturation of the red blood cells is produced by the interaction of the extrinsic and the intrinsic factor. The resultant product is absorbed from the intestine, stored in the liver and released to the body tissues for utilization as needed. Macrocytic anemia will result if there is a disturbance of any of the factors involved in this mechanism.

Wills and her co-workers [69] produced macrocytic anemia in monkeys fed a deficient diet. The anemia was then treated with various crude products and refined extracts prepared from liver, yeast (marmite) and wheat germ. In view of the fact that the "monkey anemia" was resistant to the highly purified extracts, whereas the crude preparations were beneficial in both pernicious and "monkey anemia," these investigators concluded that, in addition to the deficient extrinsic factor, some other substance, perhaps related to the vitamin B complex, was the causative agent in the production of "monkey anemia." Nine patients

65. Rozendaal, H. M., and Washburn, R. N.: Gastric Secretion in Cases of Pernicious Anemia, Ann. Int. Med. **11**:1834, 1938.

66. Kugelmass, I. N.: The Anemias in Digestive Diseases of Children, Arch. Pediat. **55**:268, 1938.

67. Vaughan, J. M.: Anaemia and the Gastro-Intestinal Tract, Brit. M. J. **2**:57, 1938.

68. Davidson, L. S. P., and Fullerton, H. W.: Some Rare Types of Macrocytic Anaemia, Quart. J. Med. **7**:43, 1938.

69. Wills, L.; Clutterbuck, P. W., and Evans, D. B. F.: A New Factor in the Production and Cure of Macrocytic Anemias and Its Relation to Other Hematopoietic Principles Curative in Pernicious Anemia, Biochem. J. **31**:2136, 1937.

with tropical macrocytic anemia were treated by Wills and Evans [4] with the preparations just described, with similar results. Whereas the highly purified products were ineffective, the crude preparations produced the expected hematologic responses. Assuming that tropical macrocytic anemia and "monkey anemia" are the same, the authors concluded that although the blood pictures of pernicious anemia and tropical macrocytic anemia cannot be differentiated, the latter disease is due to some other cause in addition to the deficient extrinsic factor. They further stated that the missing substance is not vitamin B_1, vitamin B_4, lactoflavin or nicotinic acid.

A comprehensive study of the tropical macrocytic anemia occurring in Macedonia was made by Fairley, Bromfield, Foy and Kondi.[70] From their observations, these investigators suggested the term nutritional macrocytic anemia and described two types—nonhemolytic and hemolytic. The latter is the more common type. It is usually present during pregnancy and lactation, although it has been observed in males. The bone marrow shows a panmyelopathic picture, characterized by erythropoiesis with megaloblastic degeneration, pathologic precursors of the white blood cells and an abnormal condition of the megakaryocytes. The peripheral blood is characterized by megalocytic anemia with spherocytosis; leukopenia, with immature white blood cells, and a decrease in the platelet count. The last-mentioned finding was considered to be the cause of the purpura which was observed in 25 per cent of the cases. The authors concluded that the anemia is the result of a diet deficient in animal protein and fat and that the hemolysis is due to the overactivity of a chronically irritated reticuloendothelial system which is working on an abnormal red blood cell.

Bachrach and Fogelson [9] removed the stomach as well as a large portion of the upper part of the small intestine from dogs. These animals were observed for two years and failed to show macrocytic anemia. Petri, Nørgaard and Bing [71] noted several interesting pathologic changes resulting from the removal of the stomach of young swine. These animals showed, after two months, itching, signs of calcium deficiency, inhibition of growth, emaciation, warty plaques, lengthening of the rear legs, bending of the back, a staggering and stiff gait, muscular atrophy, severe microcytic anemia and terminal diarrhea. The central nervous system showed varied degenerative phenomena, especially in the spinal ganglions, but little in the peripheral nerves. It was concluded from these results that there is a specific substance in the stomach of swine,

70. Fairley, N. H.; Bromfield, R. J.; Foy, H., and Kondi, A.: Nutritional Macrocytic Anaemia in Macedonia: A Preliminary Report, Tr. Roy. Soc. Trop. Med. & Hyg. **32**:132, 1938.

71. Petri, S.; Nørgaard, F., and Bing, J.: Pathological Changes Produced by Gastrectomy in Young Swine, Am. J. M. Sc. **195**:717, 1938.

dog and man which is required to maintain the skin and nervous system in a normal healthy state. Changes in the blood occurring in man following gastric resection were studied by Jura.[72] It is this investigator's opinion that not only is the stomach a factor in controlling erythropoiesis but, in addition, the absorption of iron and the vicarious hemopoietic function of the small intestine are also very important.

Bianco and Jolliffe[73] studied the blood of 184 alcoholic addicts. Approximately 86 per cent had polyneuritis, pellagra, stomatitis, alcoholic encephalopathy, hepatic cirrhosis or anemia. In the 25 cases of noncomplicated alcoholic addiction, no anemia was noted. In 61 per cent of the cases in which there were complications, anemia was observed. Macrocytosis occurred in 50 per cent of both groups. The authors concluded that there was no correlation between the frequency of macrocytosis and achlorhydria, the severity of hepatic damage and the presence of an enlarged liver and that the macrocytosis was due to an extrinsic deficiency with respect to normocytosis and not to hepatic failure.

Macrocytic anemia related to pregnancy has been reported by Dockeray[74] and Atkin.[75] It is the former's opinion that the anemia is due to both the pregnancy and a dietary deficiency. Adams and McQuarrie[76] reported the case of a 2 year old girl with macrocytic anemia and temporary achlorhydria. After antianemic therapy the blood picture returned to normal and remained there. These investigators suggested that the anemia resulted from a transient functional disturbance in the mechanism involved in the elaboration and utilization of the intrinsic factor.

Richardson[77] observed the occurrence of macrocytic anemia in a patient after enteroenterostomy was performed. The anemia was readily controlled by parenteral therapy. A permanent cure was effected by a second operation, which eliminated the short-circuiting of the bowel.

72. Jura, V.: La variazioni dell'eritrocitosi dopo resezione gastrica per ulcera duodenale, Policlinico (sez. chir.) **45**:31, 1938.

73. Bianco, A., and Jolliffe, N.: The Anemia of Alcoholic Addicts: Observations as to the Role of Liver Disease, Achlorhydria, Nutritional Factors and Alcohol on Its Production, Am. J. M. Sc. **196**:414, 1938.

74. Dockeray, G. C.: Puerperal Megalocytic Anaemia, Irish J. M. Sc., March 1938, p. 126.

75. Atkin, I.: Post-Partum Macrocytic Anemia Associated with Confusional States, Lancet **1**:434, 1938.

76. Adams, J. M., and McQuarrie, I.: Severe Functional Anemia in a Child, Resembling Pernicious Anemia of Adults: A Case Study, J. Pediat. **12**:176, 1938.

77. Richardson, W.: Pernicious Anemia Due to Enteroenterostomy. New England J. Med. **218**:374, 1938.

Suarez [78] reviewed 150 cases of sprue and summarized his observations concerning the red blood cells. The average mean corpuscular volume was 123 cubic microns, the color index 1.22, the volume index 1.39, the mean corpuscular hemoglobin value 36.6 micromicrograms, the hemoglobin value 66 per cent and the red blood cell count 2,710,000 per cubic millimeter. The bone marrow was normoblastic, although megaloblasts were present. The author believes that sprue is primarily a blood dyscrasia.

Several experiments were performed by Schiff and his colleagues [18] to determine the presence or absence of the hemopoietic principle in the liver of patients who clinically had exhibited macrocytic anemia. Their conclusions substantiated the work of other investigators, who had previously demonstrated the presence of the active principle in the diseased liver. Schalm,[79] employing the diffraction method of measurement of red blood cells, observed macrocytosis when damage to the hepatic parenchyma was present.

Achrestic anemia from a clinical and hematologic point of view has been carefully reviewed by Wilkinson.[80] Some cases of anomalous hyperchromic anemia have been reported by Israels and Wilkinson.[81] These authors have pointed out the various characteristic changes in the bone marrow which occur in aleukemic leukemia, aplastic anemia and achrestic anemia and how they may be differentiated from the other types of macrocytic anemia. Zanaty [82] also has studied the bone marrow in cases of achrestic anemia and has stated that this disease is not a distinct clinical entity but rather a form of aplastic anemia.

The type of treatment necessary to alleviate the various macrocytic anemias has been thoroughly summarized by Bell.[83] If the intrinsic or extrinsic factors are absent, oral medication may be effective; however, if there is a disturbance in absorption or storage, parenteral therapy should be instituted. Specific treatment should also be given for any other deficiencies which may exist.

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78. Suarez, R. M.: Clinical and Hematological Review of Sprue Based on the Study of One Hundred and Fifty Cases, Ann. Int. Med. **12**:529, 1938.

79. Schalm, L.: The Average Red Blood Cell Diameter in Liver Disease and Jaundice, Acta med. Scandinav. **93**:512, 1938.

80. Wilkinson, J. F.: L'anémie achrestique, Rev. belge sc. méd. **10**:191, 1938.

81. Israels, M. C. G., and Wilkinson, J. F.: Some Anomalous Hyperchromic Anaemias, Lancet **2**:362, 1938.

82. Zanaty, A. F.: Sternal Puncture in Pernicious and Achrestic Anaemia, Lancet **2**:1365, 1937.

83. Bell, J. A.: The Modern Treatment of Pernicious Anaemia and Associated Macrocytic Anaemias, South African M. J. **12**:547, 1938.

HEMOLYTIC JAUNDICE

The various types of hemolytic jaundice have many common features, but it is often difficult to determine the cause. The usual characteristics of the congenital type are anemia, enlargement of the spleen, jaundice, a history of exacerbations and remissions, microcytosis, spherocytosis, increased fragility of the red blood cells and constant reticulocytosis. Dyke and Young [84] described 6 cases of macrocytic hemolytic anemia, which is thought by them to be a distinct clinical entity. In spite of the fact that it has many features similar to the congenital type, it differs in that there is no family history of the disease, the anemia usually occurs after the age of 30 years, the red blood cells are large and there is a poor response to splenectomy. Israels and Wilkinson [85] observed the clinical course of hemolytic jaundice occurring in adults. They pointed out that in their series the outstanding feature was an unusual histiocytic reaction in the spleen. Two cases of acute hemolytic anemia in which a ready response to transfusions was obtained were reported by Greenwald.[86] It is the author's opinion that the disease is due to the introduction or evolution of some hemolytic substance in the blood. He based this assumption on the fact that the bone marrow appeared normal.

A similar conclusion based on experimental work was suggested by Dameshek and Schwartz.[87] These investigators discovered isohemolysins of the immune body type in 3 cases of acute hemolytic anemia. A serum possessing similar immunologic properties was prepared by the injection of red blood cells from guinea pigs into rabbits. By injection of variable doses of this hemolytic serum into experimental animals, several types of hemolytic anemia were produced. Examination of the blood revealed microspherocytosis, increased fragility of the red blood cells, reticulocytosis and "pseudomacrocytic" blood pictures. The authors believe that the spherocytosis is due to the hemolysins and not to any abnormal anatomic peculiarities or to a disturbed formation of the red blood cells in the bone marrow. They added that the hemolytic syndromes are due to the hemolysins (endogenous origin), possibly of different types, varying in amounts and acting differently in degree; the

84. Dyke, S. C., and Young, F.: Macrocytic Haemolytic Anaemia Associated with Increased Red Cell Fragility, Lancet **2**:817, 1938.

85. Israels, M. C. G., and Wilkinson, J. F.: Haemolytic (Spherocytic) Jaundice in the Adult, Quart. J. Med. **7**:137, 1938.

86. Greenwald, H. M.: Acute Hemolytic Anemia, Am. J. M. Sc. **196**:179. 1938.

87. Dameshek, W., and Schwartz, S. O.: Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias, with Particular Reference to Nature of Spherocytosis and Increased Fragility, Am. J. M. Sc. **196**:769, 1938; The Presence of Hemolysins in Acute Hemolytic Anemia: A Preliminary Note, New England J. Med. **218**:75, 1938.

resulting changes in the blood are dependent on the hemolysins, their nature and amount, and the reaction to them.

Acquired hemolytic jaundice, with its various characteristic diagnostic features, has been reported on by Rastetter and Murphy.[88] They have pointed out that the onset is abrupt, the course rapid, the cause usually not known and remissions not unusual. Pain and fever differentiate it from the congenital type. The blood findings are the same as those observed in familial acholuric jaundice. Hemolytic anemia resulting from sulfanilamide therapy was not noted by Wood [89] and by Lockwood and his co-workers.[90]

Pepper [91] has made an excellent survey of the so-called hemolytic anemias and has stated that it is difficult to differentiate them. He has suggested that they be classified according to the mechanism of production, namely: (1) a fault in the erythrocyte, (2) parasitic destruction, (3) an allergic reaction, (4) a chemical, (5) a bacterial toxin, (6) some unknown mechanism (7) specific hemolysins, (8) physical agents, (9) overactivity of the reticuloendothelial system and (10) phagocytosis.

In recent years spherocytosis and the size of the red blood cells have received considerable attention. In view of the globular form the red blood cells in hemolytic jaundice, the majority of them are near the point of hemolysis and readily exhibit this tendency when placed in hypotonic saline solution. Dacie and Vaughan [92] have carefully studied the various intrinsic and extrinsic factors which influence the fragility of the red blood cells. Of the intrinsic factors, the relation of the mean corpuscular thickness to the mean corpuscular diameter and the chemical composition of the cell and its membrane are the most important. The extrinsic factors which influence the fragility are the oxygen and carbon dioxide content of the blood, the temperature and p_H of the hemolytic solution and the concentration of the red blood cells. Hill [93] has also made careful observations on the dimensions of the

88. Rastetter, J. W., and Murphy, F. D.: Acquired Hemolytic Jaundice, Am. J. Digest. Dis. & Nutrition **4**:805, 1938.

89. Wood, W. B.: Anemia During Sulfanilamide Therapy, J. A. M. A. **111**:1916 (Nov. 19) 1938.

90. Lockwood, J. S.; Coburn, A. F., and Stokinger, H. E.: Studies on the Mechanism of the Action of Sulfanilamide: I. The Bearing of the Character of the Lesion on the Effectiveness of the Drug, J. A. M. A. **111**:2259 (Dec. 17) 1938.

91. Pepper, O. H. P.: A Survey of the So-Called Hemolytic Anemias, Ann. Int. Med. **12**:796, 1938.

92. Dacie, J. V., and Vaughan, J. M.: The Fragility of the Red Blood Cells: Its Measurement and Significance, J. Path. & Bact. **46**:341, 1938.

93. Hill, J. M.: Dimensions of the Red Cells in Familial Hemolytic Anemia, with Particular Reference to Atypical Cases, J. A. M. A. **111**:2179 (Dec. 10) 1938.

red blood cells in familial hemolytic anemia. He concluded that microcytosis and spherocytosis were present in more than 75 per cent of the cases; spherocytosis may be absent in the presence of complications (cirrhosis of the liver); macrospherocytosis may occur during a crisis, and there is no significant correlation between the globular form of the cell and the severity of the disease, the onset of the crisis, the rapidity of regeneration or the effect of splenectomy.

In a series of well controlled experiments, Rhoads and his colleagues [94] demonstrated the hemolytic effect of indole on dogs fed normal diets and the increased susceptibility of the red blood cells to hemolysis in dogs fed deficient diets and indole. Observations were made on the total amount of bile excreted and the various changes which occurred in the peripheral blood. By this method a fairly accurate index was established concerning the amount of hemolysis which was produced. Josephs [95] has made some interesting observations on patients with various types of hemolytic anemia. He studied the course of the disease (crisis) by the method of balancing blood formation (reticulocytosis) against blood destruction (urobilin excretion expressed in relation to the total circulating hemoglobin). After a sudden increase in the rate of hemolysis, there is usually a delay in a compensatory increase in erythropoietic activity, which accounts for one factor in the severity and prolongation of the crisis. From an analysis of his cases and those reported in the literature there appear to be two factors which influence the rapidity with which increased activity occurs. The first is dependent on antecedent activity (congenital type), which tends to shorten the period of delay. The second element is the nature of the hemopoietic disturbance, which may lengthen the period or prevent a response.

After transfusions which tended to terminate the activity of an acute hemolytic process, Josephs [96] noted a decrease in the urobilin content of the stools and often an increase in the red blood cell count. The latter event does not always occur. The author interpreted this finding as denoting a plasma substance which influences hemolysis. It is not soluble in ether and appears to be effective in minute amounts. When a similar substance prepared from pig's plasma [97] was used in 4 cases, conflicting results were obtained.

94. Rhoads, C. P., and Barker, W. H.: The Hemolytic Effect of Indol in Dogs Fed Normal Diets, J. Exper. Med. **67**:267, 1938. Rhoads and Miller.[15] Rhoads, Barker and Miller.[16]

95. Josephs, H. W.: Studies in Haemolytic Anaemia: I. Haemolysis, Compensatory Regeneration and Erythroblastosis, Bull. Johns Hopkins Hosp. **62**:25, 1938.

96. Josephs, H. W.: Studies in Haemolytic Anaemia: II. The Presence of an Anti-Haemolytic Factor in Human Plasma, Bull. Johns Hopkins Hosp. **62**: 53, 1938.

97. Josephs, H. W., and Winocur, P.: Studies of Haemolytic Anaemia: III. Pig's Plasma as a Source of Anti-Haemolytic Factor, Bull. Johns Hopkins Hosp. **62**:70, 1938.

In view of the multiple causes of hemolysis, it is necessary to determine the exact cause before therapy can be instituted. Transfusions are often invaluable before and after operation, but, as pointed out by Sharpe and Davis,[98] the hemolytic process may be exaggerated by this therapeutic procedure. In the congenital type, splenectomy is indicated, and, as suggested by Anderson,[99] the purpose of the operation is to restore the balance between production and destruction of red blood cells.

SICKLE CELL AND ERYTHROBLASTIC ANEMIA

According to Josephs,[95] in studying hemolytic anemia, in which he included the sickle cell variety, it is necessary to measure the rate of formation and destruction of blood. The urobilin excretion in the stools can be used as an index of blood destruction and the number of reticulocytes in the circulating blood as an indication of blood formation. The validity of these indexes is questioned by some for the following reasons: 1. With a rising hemoglobin value, it is possible that some products of pigment catabolism may be utilized in the body to form hemoglobin. If this occurred, the urobilin excretion would not be an accurate index of blood destruction at these times. 2. If the presence of erythroblasts indicates difficulty on the part of the hemopoietic system in maturing red blood cells, the reticulocyte count might not be an accurate index of the formation of red blood cells.

While there is no definite proof that excretion of urobilin measures blood destruction, it can be said that in individual cases it acts as if it were approximately proportional to the rate of blood destruction. It must be admitted that hemoglobin or its precursors may be produced more rapidly than they can be utilized. When this occurs they would be excreted as excess pigment products. Obviously, under such conditions the urobilin value would not be an index of erythrocytic destruction. Another possibility which would vitiate the urobilin value as an index of blood destruction is that erythrocytic destruction might occur before the cells entered the circulation. Nevertheless, Josephs in reporting his work, based it on the proposition that urobilin excretion measures blood destruction and believes that this explains adequately the fluctuations in the values for erythrocytes and hemoglobin.

He believes not only that there is a relation between blood destruction as indicated by urobilin excretion but that blood formation may be measured by the percentage of circulating reticulocytes. This relation,

98. Sharpe, J. C., and Davis, H. H.: Severe Reactions Following Transfusion in Hemolytic Jaundice: Report of Two Cases, J. A. M. A. **110**:2053 (June 18) 1938.

99. Anderson, P. M.: Anaemia Cured by Splenectomy, M. J. Australia **1**:385, 1938.

however, is "completely shattered" by the presence of erythroblasts. Erythroblastosis, "while often associated with greatly increased hemolysis, is not strictly dependent upon the rate of blood destruction, but constitutes a third variable and is an expression of a pathological process which affects maturation of red cells, and by so doing disturbs the ability of the erythropoietic tissue to respond effectively to the need for red cell replacement." Erythroblastosis may well be in part due to an increased need for blood formation, but it must also be considered as evidence of a disturbance of erythropoietic function.

In patients with sickle cell anemia and congenital hemolytic jaundice, the blood becomes stabilized at a constant level for long periods. In sickle cell anemia this equilibrium is less stable and at a lower level, so that the patient is more incapacitated.

It is believed by Josephs that in congenital hemolytic jaundice the process is predominantly hemolytic, whereas in Mediterranean anemia it is predominantly erythroblastic; sickle cell anemia is considered as occupying an intermediate position between the two. In a study of crises in hemolytic anemia, it was found that after a sudden increase in hemolysis, there was usually a delay in erythropoietic activity which was an important factor in the severity and duration of a crisis. This delay appeared to be influenced by (1) antecedent activity, which apparently shortened it, and (2) a hemopoietic disturbance, which might prolong it.

In a second paper Josephs [96] studied an antihemolytic factor in human plasma. This study had its inception in a "more or less" chance finding that after a patient with sickle cell anemia had been given a transfusion, there was a striking decrease in the excretion of urobilin. His studies indicated that normal plasma contains a substance which reduces the rate of blood destruction in sickle cell anemia and probably in congenital hemolytic jaundice. This substance is present in the ether-soluble fraction of protein-free plasma and is effective in minute amounts. It is suggested that in sickle cell anemia and perhaps in congenital hemolytic jaundice this substance may be lacking, and as a result the normal equilibrium between blood formation and blood destruction is disturbed.

A third paper, by Josephs and Winocur,[97] is concerned with a study of pig's plasma as a source of the antihemolytic factor. The material utilized was prepared as follows: The proteins of pig's plasma were precipitated with 95 per cent alcohol; the alcoholic solution was evaporated in a vacuum; the residue was extracted with alcohol, concentrated, filtered and evaporated to dryness, and the lipoids were extracted with ether. The residue was then taken up with alcohol. This alcoholic solution was then concentrated and administered intramuscularly. The value of urobilin excretion, in milligrams per gram of hemoglobin, was utilized as an index of the value of the preparation in controlling hemolysis. It was considered that the normal excretion is between 0.2

and 0.4 mg. per gram of hemoglobin and that an excretion of 5 mg. indicates a moderate degree of hemolysis in sickle cell anemia; an excretion of 10 to 15 mg., a relatively severe process, and excretions of over 20 mg., an extremely severe hemolysis, typical of a hemolytic crisis. Studies of the effect of injection of this substance were made on 4 patients with sickle cell anemia. Some of them showed "a good therapeutic effect," and it is hoped that in the future these plasma concentrates will be found to be more effective.

Weil [100] described Fanconi's anemia in 2 brothers, aged 7 and 13 years, respectively. The symptoms differed from those of addisonian pernicious anemia in that there was no increased bilirubinemia, achlorhydria was absent after injection of histamine and improvement did not result from liver therapy. One of the brothers showed endocrine disturbance with obesity, possibly associated with a hypophysial or thymic pathologic condition. A third, sporadic case, in a girl of 6 years, was described. Anemia and leukopenia were accompanied by pigmentation of the skin, congenital malformation of the thenar eminences and obesity (trunk).

Hellman and Hertig [101] studied the placentas of 16 infants suffering from erythroblastosis of the hydropic variety and 7 of the icterus gravis type. Pathologic changes in the epithelium, stroma and vascular tree were present in the placentas in both varieties but were less advanced in the placentas of infants suffering from erythroblastosis of the icterus gravis variety. The changes are considered specific for these diseases.

CHANGES IN THE BLOOD ASSOCIATED WITH INFECTION

Although the interpretation of the changes in the blood associated with infection has been of extreme importance clinically, little is known concerning the production of the anemia which is often present. The anemia may be macrocytic or microcytic, the latter being the more common type. Cases of acute hemolytic anemia have been reported by Baxter and Everhart,[102] Mendels,[103] Greenthal [104] and Tangredi.[105] All

100. Weil, P. E.: Myélose aplasique infantile familiale avec malformations et troubles endocriniens: Contribution à l'étude du syndrome de Fanconi, Sang **12**:369, 1938.

101. Hellman, L. M., and Hertig, A. T.: Pathological Changes in the Placenta Associated with Erythroblastosis of the Fetus, Am. J. Path. **14**:111, 1938.

102. Baxter, E. H., and Everhart, M. W.: Acute Hemolytic Anemia (Lederer Type), J. Pediat. **12**:357, 1938.

103. Mendels, J.: Acute Hemolytic Anemia (Lederer), Nederl. tijdschr. v. geneesk. **82**:536, 1938.

104. Greenthal, R. M.: Acute Hemolytic Anemia Developing During Streptococcus Sepsis: Report of a Case in Which Sulfanilamide Was Given After Anemia Had Developed, J. Pediat. **12**:517, 1938.

105. Tangredi, G.: Anemia emolitica sub-acuta febbrile, a tipo pernicioso e con epato-splenomegalia (forma del Lederer?), Haematologica **19**:171, 1938.

these authors are in agreement as to the clinical course of the disease. Persons of any age or of either sex may be afflicted. The onset is usually sudden and characterized by headaches, gastrointestinal upsets, abdominal pain and, after an incubation period of two to six days, severe anemia, pallor, icterus and fever. Splenic [106] or hepatic enlargement may or may not be present. The anemia is of the macrocytic type, with evidence of regeneration. The cause of the disease has not been definitely established. Infection has been considered by the majority [107] to be the fundamental cause, although Baxter and Everhart [102] suggested the possibility of allergy.

The accepted form of treatment is by means of multiple transfusions. Greenthal described the successful use of sulfanilamide as well as transfusions in his case and pointed out the fact that sulfanilamide may prolong the anemia and should be administered with care.

Shiskin and Gloyne [106] studied the importance of anemia as a predisposing factor in tuberculosis. Rabbits were made anemic by bleeding and then infected with human and bovine tubercle bacilli. Appreciable differences in the animals with and without anemia were not observed.

The clinical importance in infection of the numerical, cytoplasmic and nuclear alterations of the neutrophils has been emphasized frequently. Watson and Sarjeant [108] have stressed the fact that in pyogenic infections the earliest changes are leukocytosis and a predominance of young neutrophils (a shift to the left). With suppuration and progression of the infection, the white blood cells are withdrawn from the circulation faster than they are produced by the bone marrow, and leukopenia results. In uncomplicated pneumonia there is a parallel increase in the total white blood cell and the polymorphonuclear leukocyte count; in complicated pneumonia the neutrophil count is relatively increased, but leukopenia is present.

Nettleship [109] produced inflammatory changes in the skin of the rabbit and observed early severe leukocytosis. Cytoplasmic changes in the neutrophils occurred within two hours. Only the leukocytes showed necrosis early. The author believes some breakdown product, resulting from the action of the injurying agent on the peripheral tissue, diffuses into the blood stream and causes leukocytosis and hyperplasia of the bone marrow.

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106. Shiskin, C., and Gloyne, S. R.: Anaemia as a Predisposing Factor in Tuberculosis, Am. Rev. Tuberc. **38**:325, 1938.

107. Mendels.[103] Greenthal.[104] Tangredi.[105]

108. Watson, C. H., and Sarjeant, T. R.: The Significance of a Low Leucocyte Count in Acute Pyogenic Infections, Canad. M. A. J. **39**:460, 1938.

109. Nettleship, A.: Leucocytosis Associated with Acute Inflammation, Am. I. Clin. Path. **8**:398, 1938.

The total white cell count not only is of diagnostic and prognostic value in infections but has been considered by many as an important aid in the study of allergic conditions. Rusten [110] has stated that the leukopenic index is of value in atopic dermatitis only as regards food. Hill and Nethery [111] have pointed out the many technical difficulties associated with the leukopenic index but are of the opinion that the test is of considerable value when properly controlled. That all authors are not in agreement as to the diagnostic value of the leukopenic index can be judged from the observations of Brown and Wadsworth,[112] as well as those of Loveless, Dorfman and Downing.[113] The first group of dissenting investigators have pointed out that there is no mathematical justification for the test. The second group of observers have noted a reduction in the total white blood cell count in nonsensitive as well as in sensitive patients. Hence, the value of the test is questionable.

ANEMIA ASSOCIATED WITH CANCER

Carcinomatosis, especially that of the vital organs, is usually associated with anemia. The anemia may be mild or severe, macrocytic or microcytic, but it is not pathognomonic, nor does it give any information as to the site or the extent of the malignant process. Leukocytosis may often be observed. Alteration of the number of platelets in the peripheral blood is not a constant feature; the number may be increased, decreased or normal.

The etiologic factors of the associated anemia are multiple. Microcytic anemia has been ascribed to a disturbance in iron metabolism (failure of absorption or chronic hemorrhage). Welch, Mayo and Wakefield [114] studied pathologic specimens of the colon on the right side, proximal and distal to the malignant process. They observed no significant changes in the mucosa, submucosa or muscular coats of the large intestine. The ileum likewise appeared to be normal on microscopic observation. Hence, it was their opinion that whatever the cause of the anemias associated with carcinoma of the bowel, they were not due to objective structural changes proximal to the lesion in the colon or in the terminal portion of the ileum with subsequent interference of the absorption of iron.

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110. Rusten, E. M.: The Leukopenic Index Test in Atopic Dermatitis, Arch. Dermat. & Syph. **37**:52 (Jan.) 1938.

111. Hill, J. M., and Nethery, E. B.: The Variations in the Leucocyte Count in Relation to the Leucopenic Index, J. Allergy **9**:371, 1938.

112. Brown, E. A., and Wadsworth, G. P.: The Leucopenic Index, J. Allergy **9**:345, 1938.

113. Loveless, M.; Dorfman, R., and Downing, L.: A Statistical Evaluation of the Leucopenic Index in Allergy, J. Allergy **9**:321, 1938.

114. Welch, C. S.; Mayo, C. W., and Wakefield, E. G.: A Histologic Study of the Intestine Proximal to Carcinoma of the Right Side of the Colon, Associated with Anemia, Surgery **2**:849, 1937.

Anemia complicating carcinoma of the pharynx and associated with dysphagia was noted by McGibbon.[115] He reported this occurrence in members of three generations of one family and stressed the fact that heredity is a most important factor. He also pointed out that dysphagia and anemia are rare in males.

Macrocytic anemia associated with gastric carcinoma may result from metastasis to the bone marrow, the coincidental existence of pernicious anemia and cancer or, as has been demonstrated by Goldhamer,[116] the failure of the malignant gastric tissue to produce the intrinsic factor. Owing to the frequent difficulty in differentiating pernicious anemia and gastric neoplasm, roentgenograms of the gastrointestinal tract are indicated as a routine. This procedure is of especial value in cases of macrocytic anemia not associated with symptoms of degeneration of the central nervous system.

ANEMIA ASSOCIATED WITH ENDOCRINE DYSFUNCTION

The anemia associated with thyroid dyscrasias has long been a subject of controversy. Many authors have observed macrocytic anemia with diminished thyroid function, while others have noted microcytic anemia. The anemia may be directly related to the dysfunction of the thyroid gland, or it may exist as an independent condition. Bomford [117] studied 10 cases of myxedema associated with anemia. He stated that the reduced number of red blood cells and the hemoglobin value are a physiologic adaptation to diminished oxygen need by the tissues, and thyroxine is not a requisite for hemopoiesis in the bone marrow. Parsons,[118] on the other hand, suggested that the thyroid hormone is necessary for red blood cell metabolism. In accordance with this view, Jaffé [119] described the pathologic changes in a case of severe aplastic anemia associated with sclerosis of the thyroid gland. The functional glandular tissue was completely replaced by dense scar tissue, and the bone marrow was aplastic.

Meyers and his co-workers [120] have carefully analyzed a series of cases of hypochromic anemia in women and have pointed out that hypo-

115. McGibbon, J. E. G.: Pharyngeal Carcinoma and Dysphagia with Anaemia Occurring in Three Generations of One Family, J. Laryng. & Otol. **53**:32, 1938.

116. Goldhamer, S. M.: Macrocytic Anemia in Cancer of the Stomach, Apparently Due to Lack of Intrinsic Factor, Am. J. M. Sc. **195**:17, 1938.

117. Bomford, R.: Anaemia in Myxoedema and the Role of the Thyroid Gland in Erythropoiesis, Quart. J. Med. **7**:495, 1938.

118. Parsons, L. G.: Nutrition and Nutritional Diseases, Lancet **1**:65, 1938.

119. Jaffé, R. H.: Severe Anemia of the Aplastic Type Associated with Sclerosis of the Thyroid Gland, Arch. Int. Med. **61**:19 (Jan.) 1938.

120. Meyers, S. G.; Price, A. H.; Mack, H. C.; Foster, L. J., and Sharp, E. A.: Chronic Hypochromic Anemia in Women: Its Gastrointestinal, Gynecologic, Endocrine and Psychiatric Features, Ann. Int. Med. **11**:1590, 1938.

thyroidism was present in approximately 50 per cent. Disregarding the controversy as to the cause of the anemia associated with myxedema, Sharpe and Bisgard [121] clearly demonstrated in thyroidectomized rabbits that the resulting anemia readily responded to thyroid medication but could not be influenced by liver or iron. Bomfort reported similar conclusions from his clinical data.

A new syndrome that is apparently related to the posterior lobe of the pituitary gland has been described by Jones.[122] The important clinical features are hypertension, hyperchromic anemia, achlorhydria and an abnormal carbohydrate tolerance. The author has attributed the altered metabolism to hyperfunction of the posterior lobe. Flaks and his co-workers [123] have offered the opinion that hemopoiesis is regulated by a hypophysial hormone. After removal of the hypophysis of rats, the bone marrow atrophied, and there was resulting anemia. These changes could be reversed with parenteral injections of hypophysial extract.

IRON DEFICIENCY

Iron Metabolism and Experimental Anemia.—In the entire field of physiology there appears to be least established information, most speculation and most divergence of opinion on the subject of iron metabolism. A reason for this lies in the attempt to treat iron as a substance included in the daily quantitative interchange between the organism and its environment. On the basis of this unsupported and unjustified assumption, balance studies have been carried out, and an effort has been made to apply the results of observations of intake and loss during periods of constant diet to the findings obtained after the administration of disproportionately large supplements of medicinal iron. An investigation of balance applied to a substance required for nutrition implies, for its validity, that such a substance is absorbed and excreted under controlling mechanisms which, in turn, are governed by the metabolic requirements of the organism or which may, as the result of disease, depart from such requirements. In the case of iron, no such controlling mechanisms have been demonstrated. Widdowson and McCance [124] studied the intake and output of iron of healthy men and

121. Sharpe, J. C., and Bisgard, J. D.: The Thyroid Gland and Hematopoiesis: II. The Effect of Thyroid Extract Liver Extract, and Iron on the Anemia of Myxedema, J. Lab. & Clin. Med. **23**:219, 1937.

122. Jones, E. I.: A New Syndrome Apparently Due to Overactivity of the Posterior Pituitary, Lancet **1**:11, 1938.

123. Flaks, J.; Himmel, I., and Zotnek, A.: La polyglobulie provoquée par les extraits de lobe antérieur d'hypophyse prouve l'existence d'une hormone hémopoietique, Presse méd. **46**:1506, 1938.

124. Widdowson, E. M., and McCance, R. A.: The Absorption and Excretion of Iron Before, During and After a Period of Very High Intake, Biochem. J. **31**:2029, 1937.

women. While receiving between 6 and 9 mg. of blood iron daily, these persons were in balance. When the oral intake was increased by dietary changes to 12 to 16 mg., the subjects remained in balance; but when 1 Gm. of medicinal iron was given daily in the form of iron and ammonium citrates, a net absorption, over a period of a few weeks, of 1.5 to 5.0 Gm. of the metal was registered. Subsequently, without loss of the previously retained iron, the subjects were in balance on diets low in iron. The same authors [125] demonstrated that when 7 mg. of iron daily was given intravenously to normal subjects, none of the metal was excreted. These observations support their hypothesis that the intestine has no power of regulating by excretion the amount of iron in the body. This conclusion has much to recommend it, although it is in disagreement with earlier experimental studies of iron excretion and with the recent work of Nakamura,[126] Kamano [127] and Chin,[128] who found evidence by microchemical methods of the epithelial excretion of iron, respectively, in the stomach, small and large intestine and cecum of rabbits after its intravenous and oral administration. The explanation of intestinal absorption of iron offered by Widdowson and McCance on the basis simply of gross imbalance between the concentration of the metal in the intestinal contents and that in the circulating blood within the intestinal capillaries explains their observation of iron retention by normal subjects when large medicinal supplements were given and is also in accord with the studies [129] on iron retention by Fowler and Barer and by Brock and Hunter but cannot be reconciled with the conclusions of Reimann, Fritsch and Schick. A recent study by Fowler and Barer [130] of the absorption of iron by patients with pernicious anemia, lead poisoning and myxedema, conditions in which, clinically, iron deficiency is believed to play no part, demonstrated a retention of from 25 to 34 per cent of the orally administered medicinal iron, an amount comparable to that retained in hypochromic anemia. On the other hand, a preliminary report by Hahn and his associates [131]

125. McCance, R. A., and Widdowson, E. M.: Absorption and Excretion of Iron Following Oral and Intravenous Administration, J. Physiol. **94**:148, 1938.

126. Nakamura, A.: Ueber die Eisenausscheidung des Magens bei erwachsenem Kaninchen, Tr. Soc. path. jap. **28**:502, 1938.

127. Kamano, M.: Ueber die Eisenausscheidung des Dünndarms und Dickdarms, Tr. Soc. path. jap. **28**:505, 1938.

128. Chin, S.: Untersuchung über die Eisenausscheidung und Eisenresorption in Coecum, Tr. Soc. path. jap. **28**:509, 1938.

129. Bethell, F. H.; Isaacs, R.; Goldhamer, S. M., and Sturgis, C. C.: Blood: A Review of the Recent Literature, Arch. Int. Med. **61**:923 (June) 1938.

130. Fowler, W. M., and Barer, A. P.: Iron Retention in Pernicious Anemia, Lead Poisoning and Myxedema, Arch. Int. Med. **61**:401 (March) 1938.

131. Hahn, P. F.; Bale, W. F.; Lawrence, E. O., and Whipple, G. H.: Radioactive Iron and Its Metabolism in Anemia, J. A. M. A. **111**:2285 (Dec. 17) 1938.

of the metabolism of radioactive iron indicated that the metal was absorbed, retained and soon utilized in hemoglobin synthesis by dogs rendered anemic by repeated bleeding but that only slight absorption occurred in the case of nonanemic dogs. The question of whether iron is absorbed solely on the basis of its concentration and chemical state within the intestine (Widdowson and McCance) or whether such absorption is governed by a mechanism responsive to the body's needs (Whipple and his associates) awaits convincing answer, but the use of radioactive iron should prove a valuable tool in the solution of this and other problems of iron metabolism.

Experimental studies of anemia related to deficient formation of hemoglobin have for some time included investigation of substances which may either affect the utilization of iron in anemia or play a direct role in the synthesis of hemoglobin. The earlier work of the investigators at the University of Wisconsin on the part played by copper in the nutritional anemia of growing rats has been extended by Potter, Elvehjem and Hart [132] to include a study of dogs. They produced anemia in growing dogs by means of exclusive milk diets and cured the anemia with iron and copper supplements. Subsequently, 2 of the dogs were depleted of iron and copper by repeated bleeding; the consequent anemia responded poorly to iron given alone in a daily dose of 30 mg., but on the addition of 4 mg. daily of copper, regeneration of hemoglobin proceeded rapidly. They found that an increase in the copper content of the blood was associated with accelerated hemopoiesis, and they concluded that copper is required by dogs for regeneration of hemoglobin. This view of the importance of copper is not shared by Hahn and Whipple,[133] who stated that no evidence of a deficiency of copper can be demonstrated in man or the dog. In the same communication these authors attacked the conception of "available iron," that portion of food iron which can be separated from the total iron content, by means of the dipyridyl reaction, as being devoid of physiologic significance. They pointed out that by this method iron salts are 100 per cent "available" but that only about 35 per cent of that given orally to anemic dogs is absorbed. However, in comment, it should be pointed out that no claim has been made that the dipyridyl test or any other chemical procedure can determine the actual absorption of orally administered iron but only that it may indicate the amount of the metal which, in appropriate circumstances, is available for absorption. The value of the dipyridyl

132. Potter, V. R.; Elvehjem, C. A., and Hart, E. B.: Anemia Studies with Dogs, J. Biol. Chem. **126**:155, 1938.

133. Hahn, P. F., and Whipple, G. H.: Iron Metabolism in Experimental Anemia: "Availability of Iron," J. Exper. Med. **67**:259, 1938.

method lies in its application to the study of the requirements for nutritional iron and not to determinations of the efficacy of preparations of medicinal iron.

Bioassay of the availability of iron in food materials, carried out on rats with "milk anemia," has failed to yield uniform results in different laboratories. An attempt has been made by Smith and Otis [134] to explain these discrepancies as due to the varying content of copper in the anemia-producing diets. They have contended that iron depletion can be complete only when copper is given during the period of development of anemia and that part of the hemoglobin response during the curative study depends on the copper supplied by the food under assay rather than on its content of available iron. Harris and Poland [135] were unable to confirm these observations and concluded from their experimental results that supplementing the basal diet with copper during the production of anemia does not significantly affect the time or the severity of iron depletion, nor does it affect the hemoglobin response to subsequent iron feeding.

Cobalt is probably concerned with the metabolism of iron in sheep in much the same manner that copper appears to function in rats. Previously recognized anemia of sheep in Australia and New Zealand, attributed to cobalt deficiency, has been described by Corner and Smith [136] as occurring in Scotland. By means of controlled experiments they demonstrated the relation of cobalt deficiency to hypochromic anemia in sheep and found that the defect could not be eliminated with copper supplements. There was no depletion of iron reserves in the anemic animals, but medicinal iron may be effective because of its contamination with cobalt.

The effect of diets low in iron on the blood of pregnant rats and their offspring was studied by Alt.[137] When receiving an exclusive diet of whole milk powder, the rats failed to become anemic during the first pregnancy, but the stores of iron were depleted. During a second pregnancy moderate anemia occurred in such animals. The members of the first litter possessed normal hemoglobin values at birth and failed to show anemia during the suckling period, but those of the second

134. Smith, M. C., and Otis, L.: Hemoglobin Regeneration in Anemic Rats in Relation to Iron Intake, with Suggestions for the Improvement of Bioassay Technic for Measuring Available Iron, J. Nutrition **13**:573, 1937; Effect of Adding Copper to Exclusive Milk Diet Used in Preparation of Anemic Rats upon Their Subsequent Response to Iron, ibid. **14**:365, 1937.

135. Harris, P. L., and Poland, G. L.: The Effect of Copper in the Production of Nutritional Anemia in Rats, Science **87**:45, 1938.

136. Corner, H. H., and Smith, A. M.: The Influence of Cobalt on Pine Disease in Sheep, Biochem. J. **32**:1800, 1938.

137. Alt, H. L.: Iron Deficiency in Pregnant Rats: Its Effect on the Young, Am. J. Dis. Child. **56**:975 (Nov.) 1938.

litter had low hemoglobin levels at birth. Iron supplements during pregnancy protected the mothers and offspring against anemia and depletion of iron reserves, whereas the addition of copper had no apparent effect on the results.

Fouts and his associates [138] maintained puppies in good health after weaning on a diet containing purified casein, thiamin, riboflavin, liver extract supplying nicotinic acid and extract of rice polishings supplying the rat antidermatitic factor, vitamin B_6. When the B_6 factor was omitted from the diet, microcytic and hypochromic anemia, together with marked systemic changes, including hepatic lipoidosis, developed in the puppies. The anemia failed to respond to iron therapy but was cured by the addition of the B_6 factor.

Anemic dogs with renal biliary fistulas were shown by Hawkins and has associates [139] to suffer impairment of their capacity for hemoglobin production. The utilization of orally administered iron salts, food iron and liver amounted to half that found to occur in anemic dogs without biliary fistulas, but the utilization of intravenously administered iron in the formation of new hemoglobin was apparently unaffected by the loss of bile. In these dogs with biliary fistulas there was no evidence of inadequate digestion or absorption of protein, since the body weight remained uniform and the clinical condition was good, but the authors believe that in such dogs the inadequate production of hemoglobin may be related to disturbance of the hepatic function.

Gastrectomy was performed on young pigs by Petri and his co-workers.[71] After an initial period of good health the animals showed, in from one to two months, progressive hypochromic and microcytic anemia, arrest of growth, and changes in the skin, skeleton and central nervous system, together with hyperglobulinemia, cirrhosis of the liver and osteoporosis.

Dobriner and Rhoads [140] found an increase in the rate of excretion of coproporphyrin I in dogs after bleeding. The rate varied with the rate of formation of coproporphyrin III as new hemoglobin. The authors concluded that coproporphyrin I is probably a by-product in the synthesis of coproporphyrin III compounds and that the rate of excretion of coproporphyrin I is probably an index of hemopoietic activity under normal conditions.

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138. Fouts, P. J.; Helmer, O. M.; Lepkovsky, S., and Jukes, T. H.: Production of Microcytic Hypochromic Anemia in Puppies on Synthetic Diet Deficient in Rat Antidermatitis Factor (Vitamin B_6), J. Nutrition **16**:197, 1938.

139. Hawkins, W. B.; Robscheit-Robbins, F. S., and Whipple, G. H.: Hemoglobin Production in Anemia as Influenced by the Bile Fistula, J. Exper. Med. **67**:89, 1938.

140. Dobriner, K., and Rhoads, C. P.: Excretion of Coproporphyrin I Following Hemorrhage in Dogs, J. Clin. Investigation **17**:105, 1938.

Nutritional Anemia of Children.—Congenital iron deficiency was studied in rats by Parsons and his associates,[141] and an analogy was drawn between their experimental observations and conditions which might be assumed to occur in infants. They found that in female rats receiving diets low in iron polycythemia and microcytosis developed but the hemoglobin values were unaltered, a picture regarded as the first stage in the evolution of anemia due to iron deficiency. The offspring of such rats showed microcytic anemia during lactation, but after weaning, if they were fed the special diet low in iron given to the mothers, the hemoglobin value became normal, polycythemia occurred and microcytosis persisted. Iron, supplemented by copper, had a curative effect on the changes in the blood. They concluded, by analogy, that anemia due to iron deficiency in human mothers may condition nutritional anemia in infants and, furthermore, that diets low in iron during pregnancy may, even in the absence of maternal anemia, lead to the same result. However, in comment, it may be stated that such an analogy is open to question, since the ratio of embryonic to maternal weight is at least three times as high in rats as in human beings and the duration of human gestation, during which the embryo may obtain iron and other materials from the maternal diet, is about twelve times as long as the period of gestation in the rat.

The earlier views of deposition of fetal storage iron in the liver as occurring at a disproportionately rapid rate during the later months of gestation have been challenged by Iob and Swanson,[142] who found a progressive increase in the total iron content of fetal liver but no change in the fetal iron per kilogram of desiccated defatted liver throughout the period of embryonic growth.

In a discussion of nutritional hypochromic anemia, Davidson and Fullerton [143] explained its presence in infancy on the basis of low birth weight. They pointed out that 80 per cent of the total iron contained within the infant's body is present in the circulating blood. The blood normally destroyed by hemolysis during the first two months of life supplies the iron stores subsequently used for the formation of new blood in response to growth needs. Consequently, the birth weight and the associated volume of blood have a much greater influence on the capacity to form new hemoglobin than is exerted by the iron stores in

141. Parsons, L. G.; Hickmans, E. M., and Finch, E.: Studies in Anaemia of Infancy and Childhood: XI. The Effect of Iron Deficient Diets on the Size of the Red Blood Cells in Rats and in the Production of Microcytic Hypochromic Anaemia in Their Offspring; a Contribution to the Study of Congenital Iron Deficiency Anaemia in the Human Infant, Arch. Dis. Childhood **12**:369, 1937.

142. Iob, V., and Swanson, W. W.: A Study of Fetal Iron, J. Biol. Chem. **124**:263, 1938.

143. Davidson, L. S. P., and Fullerton, H. W.: Chronic Nutritional Hypochromic Anaemia, Edinburgh M. J. **45**:1, 1938.

the liver at the time of birth. Infections, according to these authors, have a deleterious effect on the formation of blood through three possible mechanisms: 1. Toxins may inhibit the formation of blood. 2. The excretion of iron may be increased. 3. The intake of iron may be reduced.

Schultz, Oldham and Morse [144] studied the iron metabolism of a normal child at three levels of iron intake, with and without supplementary crystalline vitamin B_1 (thiamin). They found the average retention of iron to be lower during periods of a high intake of vitamin B_1, and they also concluded that for an optimum intake the child requires no more than 0.8 mg. of iron per kilogram per day.

Hemoglobin estimations were obtained by Colver [145] for 310 children of preschool age from the poorer classes residing in the south London area. An incidence of 10 per cent of anemia up to the age of 3 years was found (hemoglobin, below 8.3 Gm. per hundred cubic centimeters; 60 per cent [Haldane]), and good results were obtained from iron therapy. However, in untreated patients the incidence and severity of anemia decreased progressively from the first to the fourth year of life and the disease was rarely found after the fourth year. A study was carried out by Blackstock and Ritchie,[146] who found slightly lowered blood values for 31 children between the ages of 1 and 5 years whom they had reason to believe had been receiving poor diets. Iron and ammonium citrates led to improvement of the blood in the absence of dietary correction. Türk [147] and Skrivaneli and Leban-Klemenc [148] obtained good therapeutic results from the use of compounds of iron and cevitamic acid in cases of anemia of prematurity, anemia associated with infection and nutritional anemias of children.

Hypochromic Anemia of Adults.—Chronic nutritional hypochromic anemia is the term proposed by Davidson and Fullerton [149] for the common anemia of middle-aged women due to iron deficiency. The two important etiologic factors responsible for such anemia, according to these authors, are inadequate intake and increased demand for iron,

144. Schultz, F. W.; Oldham, H., and Morse, M.: Effect of Vitamin B_1 on the Iron Retention of a Normal Infant, Am. J. Dis. Child. **56**:735 (Oct.) 1938.

145. Colver, T.: Anemia in Preschool Children: Its Incidence in South London, Lancet **1**:245, 1938.

146. Blackstock, E., and Ritchie, J. M.: Effect of Iron Administration in Cases of Subnutrition, Brit. M. J. **1**:512, 1938.

147. Türk, E.: Ce-Ferro bei Kinderanämien, Med. Klin. **34**:776, 1938.

148. Skrivaneli, N., and Leban-Klemenc, S.: Die Eisentherapie sekundärer Anämien im Kindesalter, Wien. med. Wchnschr. **88**:1161, 1938.

149. Davidson and Fullerton.[143] Davidson, L. S. P., and Fullerton, H. W.: Chronic Nutritional Hypochromic Anemia: II., Edinburgh M. J. **45**:102, 1938; III., ibid. **45**:193, 1938.

and evidence is presented that direct dietary deficiency may play a principal part in its causation. They found an average daily intake of iron for women of the poorer classes of 7.3 mg. Of this they considered 75 per cent to be "available." They assumed that only half the available iron is absorbed, yielding an average daily absorption of only 2.5 mg. Davidson and Fullerton do not attribute to achlorhydria an important influence on iron absorption through its effect on the reaction of the contents of the small intestine but believe that in the absence of hydrochloric acid the liberation of dietary iron may be reduced. A vicious circle may be created in which long-continued dietary deficiency results in defective gastric secretion with achlorhydria as well as in anemia; the gastritis so produced then leads to digestive disorders, which further aggravate the effects of an inadequate diet. Diet therapy is valuable in the prevention but not in the treatment of chronic nutritional hypochromic anemia, and iron is most efficaciously administered in the form of its ferrous salts.

The tendency of the type of hypochromic anemia under discussion to occur in successive generations of the same family has been emphasized by Lundholm,[150] who has given case reports and inheritance charts. The disorder is characterized by specific changes in the blood and bone marrow but is not necessarily associated with achlorhydria, since, in the author's view, disturbance of gastric secretion usually follows the development of anemia. Thiele and Kühl [151] believe that such anemia is a definite entity dependent, in part, on constitutional predisposition. Achlorhydria, according to their observations, is frequently present among the antecedents of patients with this form of anemia, but the etiologic role of achlorhydria cannot be proved. The disease is characterized by hypochromic and microcytic forms of anemia, atrophy of the mucous membranes of the upper part of the digestive tract, frequently leading to dysphagia, changes in the nails and paresthesias. Concomitant features which are of secondary diagnostic importance are the high degree of limitation to the female sex, the frequency of achlorhydria and the common finding of moderate enlargement of the spleen. The authors have advocated the use of iron in large doses as the most effective form of therapy for this disorder, and they consider iron ascorbate as of value and importance.

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150. Lundholm, I.: Ueber den Erbgang bei Anaemia hypochromica essentialis (achylica et non achylica), Acta med. Scandinav., 1938, supp. 89, p. 157.

151. Thiele, W., and Kühl, H.: Ueber die essentielle hypochrome Anämie: Pathogenese, Klin. Wchnschr. **17**:1137, 1938; Symptomatologie mit besonderer Berücksichtigung des Plummer-Vinson-Syndroms, ibid. **17**:1191, 1938; Therapie, ibid. **17**:1219, 1938.

Waldenström [152] discussed the etiologic role of iron deficiency, or sideropenia, in disturbances of the epithelium even in the absence of anemia. He reported 3 cases of koilonychia without anemia in which iron therapy was of benefit, and he stated that certain lesions of the mucous membrane may respond favorably to such treatment. He suggested that plasma iron determinations may serve to disclose sideropenia in patients who have no anemia. Bode and Heyrodt [153] reported on 200 patients with chronic hypochromic anemia observed over a ten year period. They concluded that in cases of general weakness, especially in association with cardiac symptoms and neurasthenia in women, studies of the blood and gastric analysis should be done. According to them the administration of iron is the only therapeutic measure of value in this form of anemia. They employed 1 Gm. of reduced iron daily and found that larger doses were unnecessary. In their experience the effect of iron was not enhanced by copper supplements. Schülten [154] emphasized that pernicious anemia and chronic hypochromic anemia may occur together, and he reported a case illustrating the coincidence of the two diseases. Study of the marrow, he stated, is a valuable procedure in the differential diagnosis. Meyers and his associates [120] reported a series of cases of chronic hypochromic anemia and discussed the multiple etiologic factors of the condition, including dietary deficiencies, achlorhydria, hypothyroidism, menorrhagia, other forms of blood loss and multiple pregnancies. Therapy, according to these authors, should include the administration of iron, attention to the diet, care of gastrointestinal and endocrine disorders and psychiatric treatment.

The influence of mucin on the absorption of iron has been investigated by Heath and his co-workers.[155] Mucin given together with relatively small amounts of iron in the form either of iron and ammonium citrates or of ferrous sulfate to patients with hypochromic anemia apparently inhibited the absorption of the metal from the intestine, as tested by study of the double-reticulocyte response. Using the same method of assay, Barker and Miller [156] secured evidence that the "Whipple liver fraction (secondary anemia fraction)" possesses some reticulo-

152. Waldenström, J.: Iron and Epithelium; Some Clinical Observations: I. Regeneration of the Epithelium, Acta med. Scandinav., 1938, supp. 90, p. 380.

153. Bode, O. B., and Heyrodt, H.: Die primäre hypochrome Anämie, München. med. Wchnschr. **85**:1306, 1938.

154. Schülten, H.: Ueber die essentielle (primäre) hypochrome Anämie, München. med. Wchnschr. **85**:1599, 1938 (Comment on article by Bode and Heyrodt [153]).

155. Heath, C. W.; Minot, G. R.; Pohle, F. J., and Alsted, G.: The Influence of Mucin upon the Absorption of Iron in Hypochromic Anemia, Am. J. M. Sc. **195**:281, 1938.

156. Barker, W. H., and Miller, D. K.: Clinical Observations on the Whipple Liver Fraction (Secondary Anemia Fraction), Am. J. M. Sc. **195**:287, 1938.

cytogenic properties apart from its content of iron. However, they found that the best clinical therapeutic results were obtained from the administration of large doses of inorganic iron. Friend [157] reported his observations on the use of iron ascorbate and concluded that the preparation gave good but not unusual results. He found, in terms of hemoglobin regeneration, that 10 mg. of iron as the ascorbate (cevitamate) was equivalent to 32 mg. of iron as iron and ammonium citrates when both were given by the intravenous route. When administered by mouth, 200 to 300 mg. of iron as the ascorbate was equivalent to 500 to 700 mg. of iron as iron and ammonium citrates, or 900 mg. as reduced iron.

A number of general articles dealing with nutritional disorders in relation to anemia have appeared in the British literature during the past year.[158] For the most part the authors have discussed the factors affecting intake, absorption and utilization of iron, as well as other substances required for hemopoiesis.

157. Friend, D. G.: Iron Ascorbate in the Treatment of Anemia, New England J. Med. **219**:910, 1938.

158. Scott, R. B.: The Iron-Deficiency Anaemias, Lancet **2**:549, 1938. Dauphinne, J. A.: Iron Requirement in Normal Nutrition, Canad. M. A. J. **39**: 483, 1938. Ungley.[2] Vaughan.[67]

(To Be Concluded)

News and Comment

Institute at University of Wisconsin.—The University of Wisconsin Medical School is to conduct an institute for the consideration of the blood and blood-forming organs, Sept. 4 to 6, 1939. The program will include papers and round-table discussions by European and American workers in the field of hematology. In addition to the discussions, the following formal papers are to be presented:

Dr. L. J. Witts, Oxford, England, Anemies Due to Iron Deficiency; Dr. Cecil J. Watson, Minneapolis, The Porphyrins and Diseases of the Blood; Dr. Cornelius P. Rhoads, New York, Aplastic Anemia; Dr. E. Meulengracht, Copenhagen, Denmark, Some Etiologic Factors in Pernicious Anemia and Related Macrocytic Anemias; Dr. Harry Eagle, Baltimore, The Coagulation of Blood; Dr. George R. Minot, Boston, Anemias of Nutritional Deficiency; Dr. Russell L. Haden, Cleveland, The Nature of the Hemolytic Anemias; Dr. Jacob Furth, New York, Experimental Leukemia; Dr. Claude E. Forkner, New York, Monocytic Leukemia and Aleukocythemic Leukemia; Dr. Edward B. Krumbhaar, Philadelphia, Hodgkin's Disease; Dr. Louis K. Diamond, Boston, The Erythroblastic Anemias; Dr. Edwin E. Osgood, Portland, Ore., Marrow Cultures; Dr. Charles A. Doan, Columbus, Ohio, The Reticuloendothelial System; Prof. Hal Downey, Minneapolis, Infectious Mononucleosis; Dr. Paul Reznikoff, New York, Polycythemia.

Physicians and others who are interested are cordially invited. A detailed program may be obtained by addressing Dr. Ovid O. Meyer, Chairman of Program Committee, University of Wisconsin Medical School, Madison, Wis.

Graduate Course in Internal Medicine.—Vanderbilt University Medical School announces a graduate course in internal medicine designed for those who desire special training in this field. The course will consist of supervised work with patients of the medical outpatient service, including the related specialties; experience in the diagnostic laboratories; assigned reading, seminars and conferences, including pathologic and radiologic conferences and autopsy study, and directed study and seminars in the preclinical sciences, particularly physiology and biochemistry. Special investigation of a particular problem in one of the divisions of internal medicine as the basis of a thesis will be required. The course will extend over a period of one year and will be open to any physician who has completed an internship, has had an additional year's experience as assistant resident in medicine or its equivalent and is acceptable to the school. The first course will begin on July 1, 1939, and is limited to 6 students. The tuition fee is $300.

Three fellowships are available for this graduate course and provide tuition, board and lodging. They are open to those who meet the requirements mentioned and will be awarded on the basis of training and recommendations. Applications for the course and the fellowships should be sent to the Director of Postgraduate Instruction, Vanderbilt University Medical School, from whom further information regarding the course and the fellowships may be obtained.

American Congress of Physical Therapy.—The eighteenth annual scientific and clinical session of the American Congress of Physical Therapy will be held on Sept. 5 to 8, 1939, at the Hotel Pennsylvania in New York. Preceding these sessions, August 30 and 31 and September 1 and 2, the congress will conduct an intensive instruction seminar on physical therapy for physicians and technicians.

Registration is limited to 100 and is by application only. Further information concerning the seminar and preliminary program of the convention proper may be procured by addressing the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.

Book Reviews

Studies on Proteinuria "Albuminuria." By J. Bing. Pp. 151. Copenhagen: Levin & Munksgaard, Ejnar Munksgaard, 1936.

The monograph is divided into four sections. In the first section the historical aspects of proteinuria are discussed, and special reference is made to the various mechanisms which produce it.

The second section describes the author's investigation of creatinine clearance as a measure of glomerular filtration. He believes that there is at present sufficient evidence that a close parallelism between the two exists but that there is not conclusive proof of it. An account is given of the special works throwing light on this subject.

The technic employed in the investigative work is explained in part 3. The author found that the total excretion of protein and albumin and thus of globulin, varies with the creatinine clearance. He points out that during protracted periods of proteinuria small quantities of proteins will make their way into the tubules, where they will be stored. In this way he explains the histogenesis of nephrosis, so that there is no question of "degeneration" in the tubules.

During the investigations patients were given 10 to 30 Gm. of urea per os, but this seemed to have no influence on the parallelism between the excretion of protein and that of creatinine or on the constant glomerular protein content. When solution of posterior pituitary or histamine was given subcutaneously the creatinine clearance and the creatinine concentration index varied. However, the parallelism between the excretion of creatinine and that of protein still existed. Brief displacements occurred in some cases, and the concentration in the glomeruli increased, probably because of the increased permeability of the glomerular membrane. The same parallelism between the excretion of the protein and that of creatinine was found in a patient who had proteinuria of the Bence-Jones type. It is impossible at present to say whether or not proteinuria is dependent on the total protein content of the blood.

There is a parallelism also between the excretion of protein and that of urea, as both keep pace with the excretion of creatinine. It was found, however, that when solution of posterior pituitary or histamine is given the proteinuria is parallel to the urea clearance only when the latter corresponds to the creatinine clearance.

The cholesteroluria also was calculated; when conditions were constant, it was found to parallel the proteinuria and the creatinine and urea clearance only when the urea clearance corresponded to the creatinine clearance. When the conditions varied there were deviations between the proteinuria and the cholesteroluria, and the amount of cholesterol and protein excreted per minute in different patients was not constant. The variation in the cholesterol content of the blood (up to 37 per cent) had no influence on the quantity of cholesterol excreted.

The inverse ratio of the urine content to diuresis applies when the creatinine concentration index changes for the tubules, but not for the glomeruli.

The determination of the relative percentage of albumin in the total protein is preferable to that of the albumin-globulin quotient in studies of the relation of albumin and globulin in the blood and the urine.

The variations in the quantity of protein in the urine in twenty-four hour specimens are discussed in section 4. The author found that the degree of proteinuria rises and falls with the protein content of the diet and that there is a rise with ingestion of the acids and in the presence of fever. The percentage of albumin in the urine remains constant during the twenty-four hours and from day to day, when the conditions are not varied, and, unlike the total protein excretion, it is not affected by the protein content of the diet, nor are the total protein content of the blood and its percentage of albumin affected.

The total excretion of protein is found to be greater in patients with nephrosis and amyloidosis than in those with glomerulonephritis and nephrosclerosis, but apparently there is no significant difference in the calculated glomerular contents in the various forms of Bright's disease. In the individual patient the degree of proteinuria varies with changes in infiltration value and glomerular permeability. The author finds almost inverse proportionality between these two values.

There seems to be no definite difference, either, in the percentages of albumin in the urine in the different types of Bright's disease. It is decreased in the late chronic stages because of a corresponding fall in the percentage of albumin in the blood or because of altered glomerular permeability. The renal factor measures this permeability, which is found in the majority of cases to be between 1 and 3. In cases of nephrosis and amyloidosis it is relatively high, and the low percentage of albumin in these cases is caused by similar conditions in the blood. In patients with chronic glomerulonephritis and contracting nephrosis it is found to be lower.

These studies are illustrated by case reports, and many tables and charts aid greatly in the interpretation of the text. This interesting monograph on an important phase of renal disorders should be of interest to every internist, as well as to investigators of renal disease.

Cardiovascular Disease in General Practice. By Terence East, F.R.C.P., London, Physician-in-Charge of Cardiological Department, King's College Hospital. Price, 10s. 6d. Pp. × +206, with 43 illustrations. London: H. K. Lewis & Co., Ltd., 1938.

There seems to be a worldwide movement afoot to educate the physician in general practice. A few years ago small books on various practical topics designed to appeal to the general practitioner were published in both France and Germany, and now a series on general practice is forthcoming from Great Britain.

In the latter part of 1934 and during the early months of 1935 there appeared in the *British Medical Journal* a group of articles dealing mainly with treatment and written by well known teachers. Later these articles were assembled in book form and published under the title, "Treatment in General Practice." There were two volumes. They were put out by H. K. Lewis and Company. They were well printed, of convenient size to fit into one's pocket and extremely readable. They were popular, too. The first edition appeared in March 1936; it was reprinted in March 1937, and a second edition came out in June 1938.

The series on general practice appears to be an offshoot of "Treatment in General Practice," elaborating in monographic form certain important topics. It, too, is published by H. K. Lewis and Company. In external appearance the volume on cardiovascular disease is almost an identical twin of the first volume of "Treatment in General Practice." The main difference is that the latter is printed on slightly smoother paper by the University Press of Glasgow and sells for 8 shillings and 6 pence, whereas Dr. East's book is printed in London by the Whitehouse Press on somewhat coarser paper and in larger type and is a trifle more expensive. By strange coincidence, the chapter on the management of auricular fibrillation and flutter in "Treatment in General Practice" was written by the same Dr. East, who now appears to have expanded this chapter into a book.

The book is readable. It repeats from a slightly different angle and from one pen what already has been told by several authors in the book on treatment. An interesting minor difference is that electrocardiography is scarcely mentioned in East's book, although in "Treatment in General Practice" the subject receives due emphasis. The author, one imagines, does not believe that many general practitioners are familiar with tracings and their interpretations, and this may be a valid assumption, despite the relative inexpensiveness of the portable machine and the frequency with which, on this side of the Atlantic at least, it is used.

The book is worth meeting. It makes a pleasant companion for a railroad journey; if the other volumes of this series are as attractive, they will embellish any medical library.

The Chemistry of the Sterids. By Harry Sobotka. Price, $8.50. Pp. 634. Baltimore: Williams & Wilkins Company, 1938.

This book consists of a correlation and systematization of the literature on the chemical and physical properties of the sterids. It is intended as a companion to the volume entitled "The Chemistry of the Bile Acids and Related Substances," which was previously published by the author, the two volumes being independent but, at the same time, overlapping in many respects.

The present volume consists of eleven chapters, which include a brief historical survey of sterid chemistry and of methods of structural research and an exhaustive discussion of the chemical and physical characteristics of the sterids. The author has included much on the hormones of sterid constitution. There is a lengthy classified catalog of the sterids and their derivatives, containing their structural formulas, systematic designations, melting points, data on optical activity and other physical constants, as well as information on their occurrence, formation and synthesis, to which are added accounts of their chemical reactions and transformations from all sources available on Jan. 1, 1937. In addition, there is an extensive bibliography of domestic and foreign literature on the sterids. The index is quite complete.

Sobotka has accumulated all the data on sterid chemistry, which existed in a chaotic state in the literature, and has admirably organized it in a simple and accurate fashion for the investigator attempting to master the extensive literature on the subject. The book should serve as an indispensable supplement to the handbooks on organic chemistry and should conserve much time for those interested in problems of sterid chemistry.

The Pneumonias. By Hobart A. Reimann, M.D., Professor of Medicine, Jefferson Medical College, Philadelphia; Formerly Professor of Medicine, University of Minnesota; Formerly Associate Professor of Medicine, Peiping Union Medical College, Peiping, China. With a foreword by Rufus Cole. Cloth. Price, $5.50. Pp. 381, with 111 illustrations. Philadelphia: W. B. Saunders Company, 1938.

Dr. Reimann has made a substantial contribution by clearly and forcibly expressing the modern points of view on the pneumonias. He constantly emphasizes the etiologic classification of the acute pulmonary infections and their specific treatments. He correctly insists that every effort must be taken to ascertain the causative organism in each case at the earliest moment. Thus pneumonia becomes an acute medical emergency requiring the facilities of a modern hospital, a good laboratory and often a clinical specialist. In a discussion of treatment, the nature of the subject requires a rather dogmatic presentation, but most views expressed here are orthodox. Some readers will wish for a more detailed discussion of oxygen therapy. With regard to the use of sulfanilamide in pneumococcic pneumonia, the author reserves judgment. He effectively disposes of many outmoded types of treatment. There is a valuable and well illustrated chapter on roentgenography. In this book the atypical, rare and mixed types of pneumonia are completely discussed for the first time.

Books like this, which have been developed from the author's experience, have a practical value not attained by more traditional presentations.

The Patient and the Weather. Volume IV, part 3: Organic Disease; Surgical Problems. By William F. Petersen, M.D., assisted by Margaret E. Milliken, M.S. Cloth. Price, $10. Pp. 651, with 482 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1938.

The material for this massive work, dealing with the effect of the weather on the human system, has been carefully compiled and painstakingly arranged. However, one must be a meteorologist to appreciate its value fully.

This book is of interest to the general practitioner as it covers such subjects as infection, inflammation, ulcers, disease of the gallbladder, pancreatitis and ectopic pregnancy. Here and there the author has added numerous graphs, which he has taken great pains to prepare.

The author considers all illnesses and pathologic conditions as due to changes in temperature, polar fronts and other meteorologic factors. This, of course, is not medically scientific, as no reference is made to the bacteriologic or to the pathologic aspects of the various conditions described.

The reviewer of this monograph cannot recommend it as a textbook. However, it is worthy of reading and rereading so that some idea can be obtained of the influence of the weather on the human system.

The Chemistry of the Amino Acids and Proteins. Edited by Carl L. A. Schmidt, M.S., Ph.D., Professor of Biochemistry, University of California. Price, $7.50. Pp. 1,031, with 260 illustrations and 152 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1938.

Sixteen collaborators in the United States and Netherlands have joined to make this the most detailed and inclusive volume in the English language dealing with the proteins. It stands as a worthy successor to the obsolete monograph of Brailsford Robertson and to Jacques Loeb's brilliant but sharply delimited work. Dealing as it does with every phase of protein chemistry, it will be welcomed as a working tool by biochemists, immunologists and many organic chemists. Practitioners of medicine, unless unusually conversant with the language of physical chemistry, will find the body of the book too difficult to read; the last two chapters, dealing with applications to immunity and nutrition, can be read with interest and profit by any physician.

Clinical Roentgenology of the Digestive Tract. By Maurice Feldman, M.D., Assistant Professor of Gastroenterology, University of Maryland; Associate Roentgenologist, Sinai Hospital; Assistant in Gastroenterology, Mercy Hospital, Baltimore. Price, $10. Pp. 1,014, with 358 illustrations and 179 tables. Baltimore: William Wood & Company, 1938.

This text presents a thorough consideration of gastrointestinal disease. It is written primarily for the roentgenologist and gastroenterologist. The author has systematically presented each subject as far as possible with regard to incidence, etiology, age and sex, site, association with other conditions, pathology, clinical diagnosis and roentgen diagnosis.

In addition to the alimentary tract, disease of the gallbladder, and cholecystography, and also pancreatic disease are especially well presented.

The literature is extensively reviewed, with inclusion of numerous references. As a whole the book is clear and thorough, it is adequately illustrated and it will be an invaluable reference work.

In compiling material for a text on as extensive a subject as this, the author is to be commended on his complete and understanding presentation.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung, Eleventh Meeting. Edited by Prof. Dr. E. Koch. Price, 11.25 marks. Pp. 430, with 131 colored illustrations, together with charts. Dresden: Theodor Steinkopff, 1938.

This issue of the proceedings of the Deutsche Gesellschaft für Kreislaufforschung consists of forty-three reports, lectures and discussions by as many different observers on the subject of circulatory collapse. The discussions include such subjects as circulatory collapse as related to internal medicine and surgery, significance of muscle tonus in postoperative shock, carbonic acid and collapse, changes in capillary permeability in the capillary beds and many other physiologic, pharmacologic and therapeutic aspects of the subject. The discussions are exten-

sive and cover the subject completely. There are many illustrations accompanying the presentations, which increase the value considerably.

This issue of the proceedings is recommended to all interested in normal and abnormal peripheral vascular physiology and also to clinicians, who so frequently encounter circulatory collapse.

Intoxications et carences alimentaires. Edited by Maurice Loeper. Price, 60 francs. Pp. 259. Paris: Masson et Cie, 1938.

This book, edited by Maurice Loeper, who was assisted by fifteen contributors, consists of sixteen chapters dealing with alimentary intoxications and deficiencies. Digestive hypersensibility, secretory insufficiencies and alimentary residues, the defense and protection of the gastrointestinal tract, micro-organisms of the gastrointestinal tract and their urinary elimination, vascular and nervous difficulties of digestive origin, cutaneous reactions of digestive origin, the effects of the avitaminoses on the gastrointestinal tract, local and general therapy of digestive insufficiency and other subjects are considered. The authors present the problems from a clinical point of view, attempting to aid the clinician with an explanation of mechanistic, diagnostic and therapeutic problems associated with intoxications and physiologic dysfunctions of alimentary origin. The significance of primary alimentary dysfunction from the patient's standpoint and its clinicial understanding are presented in a simple and clear fashion.

The book is recommended to internists and especially gastroenterologists, who frequently encounter such alimentary problems in their clinical endeavors.

A Biological Approach to the Problem of Abnormal Behavior. By Milton Harrington. Price, $4. Pp. 459, with 12 illustrations. Lancaster, Pa.: The Science Press Printing Co., 1938.

The importance of the psychologic element in disease is being more and more emphasized and rightly so. Every physician soon learns that the majority of his patients have no gross anatomic lesion; they suffer because of an abnormal reaction to a situation which either is entirely environmental or perhaps has some slight physical basis. A good many books have appeared recently dealing with the problems of disease from this standpoint, of which this is one. The reviewer does not feel qualified to criticize the soundness of this particular writer's point of view, but the book is interesting; and thinking along these lines is undoubtedly profitable for every physician who seeks to go beyond the old approach of explaining his patients' troubles in terms of morbid anatomy.

Pseudo-Tuberculosis in Man. Part I: Besnier-Boeck's Disease. By Prof. I. Snapper and Dr. A. W. Pompen. **Part II. Regional Ileitis.** By Prof. I. Snapper. Price, Hfl. 7.50. Pp. 90, with 13 illustrations. Haarlem, Netherlands: de Erven F. Bohn, 1938.

This handsome volume with its beautiful illustrations, contains lectures given by Professor Snapper at the University of London on the sarcoids of Boeck and on regional ileitis. In addition to general descriptions there are interesting detailed case reports. The discussion emphasizes especially the differentiation of these conditions from true tuberculosis.

Klinische Infektionslehre: Einführung in die Pathogenese der Infektionskrankheiten. By Dr. Felix O. Höring, Oberarzt der II. medizinischen Klinik und Dozent an der Universität München. Price, 10.50 marks. Pp. 184. Berlin: Julius Springer, 1938.

This book is a clinical presentation of the subject of infectious diseases, largely in a textbook manner, and would be suitable for use by medical students. It does not seem to contain anything that would be of special interest to specialists in bacteriology or clinical pathology.

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